Table of contents: Chapters 6-10

6 Review of psychological therapies for depression

6.1 Introduction

It has long been recognised that people with depression can be helped by focusing on their psychology. For example, the early Greek physicians noted the value of helping depressed people come to terms with grief, increase their levels of activity and the use of persuasion (Jackson, 1986). In the East a variety of old traditions have emphasised the importance of 'mind training' as an antidote to depression and other difficulties (Sheikh & Sheikh, 1996), techniques now being explored for relapse prevention (Teasdale et al., 2002). However, it has only been in the last century that different formal 'psychotherapies' have been developed (Ellenberger, 1970; Ehrenwald, 1976). These have proliferated rapidly (Roth & Fonagy, 1996). In addition there has been a vast expansion of different *theories* about the causes, vulnerabilities and maintenance factors for depression (Gilbert, 1992). More recent has been the development of psychological therapies designed *specifically for depression*, linked to specific theories, and the use of randomised control trials for assessing efficacy (Wampold, Minami, Baskin & Tierney, 2002). The focus of this guideline is on those approaches for which there is some evidence of efficacy and are routinely used in the NHS..

6.1.1 What was known before

In their systematic review of a large number of studies, Roth and Fonagy (1996) concluded that there was good evidence for some psychological interventions for a range of psychological disorders, including depression. Many reviews have found that psychological treatments specifically designed for depression (e.g., cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT)) to be equivalent to drugs in terms of efficacy (DeRubeis et al., 1999; Hollon et al., 2002). Recently, the Health Technology Assessment Group published a *Systematic Review of Controlled Trials of the Effectiveness and Cost Effectiveness of Brief Psychological Treatments for Depression* (2001). Their general finding was that psychological therapies were effective, with 50% or more of those taking part having recovered by the end of treatment. However, they caution that a sizeable proportion of this may be due to non-specific factors, such as the therapeutic relationship and natural time course of depression. No significant differences were found between treatments that were specifically designed for depression, such as cognitive therapy, behavioural therapy and interpersonal therapy (page 23) (a finding similar to Wampold et al., (2002)) although they included non-RCTs and did not compare psychotherapies with pharmacological treatments.

However, they note that many studies that obtain this result often use participants recruited via media advertising and this affects outcome (p.16).

Although non-specific therapies tend to perform less well than specific therapies Leichsenring's (2001) meta-analytic study on the comparative effects of short-term cognitive behavioural therapy and psychodynamic therapy found little evidence of difference. This may be a result of large numbers of patients who respond in trials independent of the nature of the intervention as a result of non-specific therapeutic factors.

In many of these reviews studies other than randomised controlled trials were included in analyses so caution should be exercised when interpreting the findings.

6.1.2 Current recommendations

In 1999, the *Clinical Standards Advisory Group* acknowledged the effectiveness of some psychological interventions for depression and advised on the need for localities to develop resources for providing such interventions. The Department of Health's *Evidence Based Clinical Practice Guideline: Treatment Choice in Psychological Therapies and Counselling* (2001) made similar recommendations. Indeed, in other countries such as USA, (Beutler et al., 2000), and Canada, (Segal et al., 2001A; Segal, et al., 2001B), guideline development groups are consistent in noting the effectiveness of psychological therapies, especially those that have been designed for depression such as cognitive behavioural therapy and interpersonal psychotherapy and recommending them as effective treatments.

6.1.3 Challenges to the assessment of evidence of what works for whom

It is now recognised that specifying the active ingredients in effective outcomes of a therapy is difficult. These difficulties are confounded by many issues relating to both the therapies themselves and other factors, including the nature of the disorder being treated. They require careful consideration when judging the evidence.

Commonalities and developments in psychological treatment

Although separate approaches can be operationalised into "pure forms", in practice most psychological treatments of depression share common features. Indeed, there has been long debate about the 'specificity verses the non-specificity' of treatment (Karasu, 1986) . Many of these common features relate to the therapeutic relationship such as providing an accepting, open and active listening relationship that helps to de-shame and remoralise people. In addition however, there have been many suggestions for psychotherapy integration (Norcross & Goldfried, 1992). Even without a deliberate attempt to integrate therapies many approaches have evolved overlapping features in focus and intervention. For example, cognitive-behavioural therapy, as the term implies, involves both cognitive and behavioural interventions and aids people's problem-solving abilities. Other developments in cognitive behavioural treatments seek to integrate cognitive and interpersonal approaches (Keller et al., 2000). Others seek to

integrate different conceptual approaches (the cognitive and the psychodynamic), such as cognitive-analytic therapy (Ryle, 1989). Within any broad approach to therapy there can be variations that differ subtly in conceptualisation, focus and technique. Nonetheless, work is proceeding to clarify specific elements of therapies and how these may or may not contribute to change process, for example, Goldfried et al., (1997) Ultimately, however, all therapies should be cognisant of the scientific research and findings on the psychological regulators of mood states. Treatments may work for reasons other than their proponents think they do.

Therapies are also constantly evolving. For example, while the early trials of cognitive therapy focused primarily on automatic thoughts and assumptions, more recently some cognitive therapists have advocated additional elements of schema focus (e.g., Young, Weinberger & Beck, 2001). Salkovskis, (2002a) has argued that, 'In most incidences, CBT for any particular psychological problem is quite different now to CBT as practised ten or even five years ago. This process is evolutionary and interactive, and pragmatic outcome trials play a relatively minor part in this development (p 1)'. Of course, the same will apply to other forms of psychological treatment. This means that treatment manuals are necessary to clarify exactly what was done in a trial. It will also direct people to specific skills needed to engage that therapy as was conducted in the trial. However, treatment manuals also have a number of disadvantages, in routine practice . First, they may restrict innovation because therapies are often in a constant process of development and change in line with new findings. (Elliott 1998). Secondly, as therapies become more complex and combine different elements in new packages, this can lead to a proliferation and an increasingly large number of different treatment manuals requiring validation Although RCTs using manualised treatments can be one (of a number) of research endeavours that lead to the evolution of therapeutic understanding and techniques, it is unclear how an uncritical use of this approach will avoid stifling innovative practice.

Therapist variables

Therapists differ in their personality, values, beliefs about the causes of depression and these may affect the outcome of treatment (Blatt et al., 1996). Therapists who take part in research studies vary in their level of training and experience, and in whether they have received basic counselling training or not. For example, cognitive behavioural training often assumes basic counselling skills (Beck et al., 1979), whereas many psychodynamic approaches may not and thus these issues are addressed as part of psychodynamic training. Some studies of psychological interventions have used comparatively untrained therapists (e.g., GPs or primary care workers) who are taught specific interventions. Graduate clinical or internship students are also often used in clinical trials. Their therapeutic practice may be untypical of routine clinical practice and their approach highly structured adhering closely to a treatment manual.

Good Practice Point
Healthcare professionals providing psychological treatment should be experienced in the treatment of the disorder and competent in the delivery of the treatment provided. (GPP)

Relationship factors
Many approaches advocate a therapeutic stance of genuineness, empathy and positive regard as derived from early counselling models of change (Rogers, 1957). Indeed, there have been important developments in understanding the role of the therapeutic relationship and alliance (Safran & Muran, 2000) and therapeutic 'universals' such as remoralisation, social support, and reassurance are also regarded as important factors for treatments (Norcross, 2002; Shaap et al., 1993). The quality of the alliance/relationship may account for a significant percentage of variance in outcome (Norcross, 2002; Roth & Fonagy, 1996). Despite this few research trials offer data on therapist characteristics or capacity to create a good therapeutic relationship.

Recommendation
In all psychological interventions healthcare professionals should develop and maintain an appropriate therapeutic alliance, because this is associated with a positive outcome independent of the type of therapy provided. (C)

Variation in the delivery of psychological treatment
Treatments can vary considerably in the mode by which they are delivered, including individual, marital, family and group. When evaluating the effectiveness of a particular intervention the effect of setting needs consideration independently of the therapeutic approach. Hence, for example, individual cognitive therapy should be tested against group cognitive therapy.

Disorder variations
Typically, the symptom-focused diagnostic approach distinguishes between types of depression (e.g., psychotic versus nonpsychotic), severity (mild, moderate and severe), chronicity, and treatment resistance. As this is the approach adopted in much contemporary research, and underpins the evidence base, it is adopted for this guideline. However, as proposed by Akiskal and McKinney (1975) nearly thirty years ago, depression is best considered a final common pathway that can have many routes into it. It is primarily a disorder of the positive affect system. There are therefore growing concerns as to adequacy of the current diagnostic system for efficacy research and the relationship between different diagnosis and different psychological and physiological processes (and indeed pharmacological interventions). For example, it is common for depressed patients to have different co-morbid diagnoses, such as social phobia, panic and various personality disorders (Brown et al., 2001), which can affect outcome. Pre-existing disorders, such as social anxiety disorders may, for example,

increase vulnerability to depression, influence treatment seeking, the therapeutic relationship, and staying in treatment.

Variations in length of therapy

A key issue in the provision of therapy is deciding on the number of sessions to be undertaken. There are at least three factors to take into account. Barkham et al. (1996) found that eight sessions of either cognitive behavioural or psychodynamic interpersonal therapy appeared to generate faster change than sixteen sessions. These authors suggest that time constraints may have speeded up engagement and work on therapy. However, different symptoms, e.g., those of distress versus those of self-criticism, appear to have a different time course. Key issues relating to the ability to form a therapeutic relationship will have an impact on time course and responses to time limited therapies (Hardy et al., 2001). Third, historical factors such as sexual abuse may significantly impact upon speed of engagement and recovery. With this in mind the GDG undertook a separate analysis of short-term psychotherapies in Section 6.10.

Patient variations

There is evidence that the effectiveness of psychotherapy designed for depression can vary extensively across individuals, with some patients making rapid gains and others changing more slowly (Roth and Fonagy, 1996; Hardy et al., 2001). Part of the reason for this is that depressed patients vary greatly in their personalities, premorbid difficulties and histories (e.g., sexual abuse), cultural backgrounds, psychological mindedness, psychological competencies and current relational and social problems - all of which may significantly affect outcomes (Sotsky et al., 1991). As noted in our introduction, socio-economic factors (e.g., poverty and unemployment) account for large variations in population rates of depression. There is some evidence that patients who are perfectionistic (Blatt et al., 1996) and highly self-critical (Rector et al., 2000) may do less well with standardised therapies. However, few studies of the psychological treatment for depression (or indeed any other type of intervention) control for patient variations.

Taken together these variations raise concern that depression may be far too heterogeneous a diagnosis in biological, psychological and social terms to enable clarity on which to develop specific and effective interventions. The data reported below are from trials that treat depression as a single disorder. However, depression is a highly heterogeneous disorder with many variables affecting outcome, including history (e.g., of child abuse) personality (e.g., perfectionism and self-criticalness) and life events. We would hope that future research might seek to be more specific on sub-typing in relation to therapy success and failure.

Recommendations

In patients with depression who have significant comorbidity consideration should be given to extending the treatment of depression with specific treatments or offering treatments that focus explicitly on the comorbid problems. (C**)**

Recruitment

The populations studied in a clinical trial can be influenced by the method of recruitment to the trial. For example, in some studies patients are recruited through

media advertisements, while in others they are recruited via routine service referral. Hence, although all patients will have met diagnostic criteria for 'depression' the settings in which recruitment takes place may exert an important influence on the type of depression treated, and patient variation. These factors can influence outcome (Churchill et al., 2001).

6.1.4 Use of RCTs in psychotherapy

RCTs for psychotherapy have been adopted from the methods of drug studies and this can raise a number of difficulties (Elliott, 1998; Roth & Fonagy, 1996). They have some disadvantages, for example they may have unrepresentative patient poplulations, limited o outcome measures, and significant problems with truly blinding assessors to the intervention. Nevertheless RCTs have a key role in developing evidence-based practice but are best seen as only one element of a complex chain which moves from initial case series through controlled trials (development studies) on to randomised control trials (efficacy studies) and beyond to their application to routine care in 'ordinary' clinical settings (effectiveness studies).These issues were born in mind by the GDG when assessing the evidence.

Despite the proliferation of psychological treatments, the number of high quality trials of sufficient statistical power is low. In addition, trial results can be hard to interpret because of poor description of the trial participants , poor control for adherence to the therapy, uncertainty about therapist training and experience and, in some cases, participants having adjunct therapy, including antidepressants, during a trial. These concerns are amongst those which have lead us to be conservative in our selection of studies considered for review.

6.1.5 Therapies considered for review

The following therapies are considered as they were seen as available in the NHS and there was initial evidence of a sufficient evidence base to warrant further investigation:

- Cognitive behavioural therapies (CBT) (for individuals and groups)
- Behaviour therapy (BT)
- Interpersonal psychotherapy (IPT)
- Problem-solving therapy
- Non-directional counselling.
- *Short-term P*sychodynamic psychotherapy
- Couples focused therapy

In addition, two sub-analyses on the whole data set were performed. One pulled together all studies undertaken exclusively on older adults with depression (mean age 65 years) and the other looked at studies of short-term psychotherapy.

6.2 Cognitive behavioural therapies (CBT)

6.2.1 Introduction

Cognitive behavioural therapy for depression was developed by Beck during the 1960s and was formalised into a treatment in the late 1970s (Beck et al., 1979). Its original focus was on the styles of conscious thinking and reasoning of depressed people. For example, when depressed, people focus on negative views of themselves, the world and future. A key aspect of the therapy is to take an educative approach where, through collaboration and guided discovery, the depressed person learns to recognise their negative thinking patterns and how to re-evaluate their thinking. This approach also requires people to practise re-evaluating their thoughts and new behaviours (called homework). The approach does not focus on unconscious conflicts, transference or offer interpretation as in psychodynamic therapy. As with any psychological treatment, cognitive behavioural therapy is not static and has been evolving and changing. For example, as noted some cognitive therapies for depression may now focus on a schema based approach (Young et al., 2001) or help depressed people evaluate the effects of their behaviour on relationships (e.g., McCullough, 2000). However, studies that have explored different 'ingredients' of CBT (e.g., behavioural activation, skills to modify automatic thoughts and schema focus) suggest that behavioural activation and thought-focused treatments may be as effective at altering negative thinking as full schema-focused cognitive behavioral therapy (Jacobson et al, 1996). The guideline refers to 'cognitive behavioural therapies' to indicate the range of approaches included in this term.

6.2.2 Definition

Cognitive-behavioural therapies were defined as discrete, time limited, structured psychological interventions, derived from the cognitive-behavioural model of affective disorders and where:

- Therapist and patient work collaboratively to identify the types and effects of thoughts, beliefs and interpretations on current symptoms, feelings states and/or problem areas;
- Develop skills to identify, monitor and then counteract problematic thoughts, beliefs and interpretations related to the target symptoms/problems;
- Learn a repertoire of coping skills appropriate to the target thoughts, beliefs and/or problem areas.

6.2.3 Studies considered for review[1]

6.2.3.1 Source of studies

The review team used the existing systematic review by Gloaguen et al. (1998) as the starting point for this section. Gloaguen et al. included 48 trials, of which 36 failed to meet the criteria set by the GDG and so were not included in this section:

- Two trials were of adolescents and therefore outside the scope of this Guideline (LEWINSOHN1990, REYNOLDS1986);
- Three were unpublished and the review team were unable to obtain full trial reports (NEIMEYER1984, ROTZER1985, ZIMMER1987);
- Twenty-four failed to meet the inclusion criteria (see table of excluded references in the Appendix 17; BECK1985, BEUTLER1987, BOWERS1990, COMAZ-DIAZ1981, DUNN1979, HOGG1988, HOLLON1992, LAPOINTE1980, MACASKILL1996, MAYNARD1993, MCNAMARA1986, PACE1993,ROSS1985, RUSH1977, SHAPIRO1982, SHAW1977, STEYER1984, TAYLOR1977, TEASDEALE1984, THOMPSON1987, WARREN1988, WIERZBICKI1987, WILSON1983, WILSON1990, ZETTLE1989);
- In two all participants had a primary diagnosis of dysthymia (DUNNER1996 and HELLERSTEIN2001)
- Two were considered in the section examining couples therapies (EMANUELS-ZUURVEEN1996, JACOBSON1991);
- Two used an intervention that did not meet the GDG's criteria for CBT (MCLEAN1979 used behaviour therapy with a small cognitive element, and SCOGIN1987 used a form of guided self-help).

New searches[2] conducted by the review team found a further 47 trials either published too recently to be included in the Gloaguen et al. (1998) review, or not identified in that review, with two more being found through checking reference lists. Thirty-two of these failed to meet the inclusion criteria set by the GDG.

In addition, two unpublished studies were identified by contacting researchers known to the GDG (Appendix 5), Freeman et al (Unpublished), which was used in the analysis and one by Steve Hollon, which was not used because a full trial report was unavailable.

Thus, 29 trials (13 from Gloaguen et al. (1998), 15 from new searches, 1 unpublished study) were included in this section: 17 from the US, 9 from the UK and 3 from Europe. In all, data from 2,940 participants were used.

---

[1] Full details of the search strategy for this and other reviews in the guideline are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17, which also contains a list of excluded studies with reasons for exclusions.

[2] Full details of the search strategy and information about each study along with an assessment of methodological quality will be included in the guideline as appendices.

6.2.3.2 Study characteristics

There were 18 studies of individual CBT for patients with a primary diagnosis of depression at baseline, six of which included follow-up data (BLACKBURN1981, BLACKBURN1997, GALLAGHER-THOMPSON1994, HAUTZINGER1994, MURPHY1984, SHAPIRO1996). A further study included a range of diagnoses at baseline with 62% having a primary diagnosis of depression (WARD2000). Since this is an important primary care-base study comparing CBT with counselling and GP care, it is included in the review of counselling and short-term psychological therapies in Section 6.10 where there is little other RCT-level evidence. Two additional studies looked at CBT for patients with residual symptoms after initial treatment (PAYKEL1999 and FAVA1994); both included follow-up. A further two studies looked at continuation treatment in treatment responders (JARRETT2001 and TEASDALE2000).

Four studies compared group CBT to other group therapies (BEUTLER1991, BRIGHT1999, COVI1987, KLEIN1984) one of BEUTLER199 included follow-up.

In most studies participants had a primary diagnosis of depression. The exception is JARRETT1999 where participants are described as having 'atypical depression' defined as '…a sub-type of MDD during which patients have reactive mood and at least 2 of the following 4 symptoms: hyperphagia, hypersomnia, leaden paralysis, or a lifetime history of interpersonal sensitivity to rejection, resulting in functional impairment' (p431). In the opinion of the GDG the definition of this did not comply with accepted criteria and was, in fact, major depressive disorder. Apart from the 'placebo plus clinical management' treatment group, where more than 50% of study participants left treatment early, data from this study were retained in the analysis.

- Studies also varied as followed:
- Baseline severity – moderate to very severe
- Therapist experience and training – from PhD students trained specifically for the study to experienced therapists
- Setting and source of patients, including inpatient, outpatient, primary care and volunteer studies
- Study length – 6 to 21 weeks
- Number of sessions – 6 to 25

6.2.3.3 Special note: the clinical management of trial participants on study medication

In many studies with an antidepressant treatment arm, medication was administered within the context of a clinical management protocol, often following the NIMH treatment manual (Fawcett, 1987). This involves twenty-minute weekly sessions with a study psychiatrist to assess clinical status and to provide a supportive atmosphere, plus access to 24-hour emergency care. This could be considered an psychosocial intervention its own right. For example, in Malt et al. (1999) a 'counselling' intervention was based on this protocol. This kind of clinical management is not analogous to routine NHS psychiatric or GP care, and should be born in mind when assessing the following results.

6.2.3.4 Comparisons

Since so many comparisons were possible from the available data, some were combined in an attempt to increase statistical power (for example, behaviour therapy and IPT were combined as 'therapies designed for depression').

6.2.4 Evidence statements[3]

6.2.4.1 Individual CBT compared with wait-list control

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring CBT over wait-list control on reducing depression symptoms at the end of treatment as measured by the BDI (N=2; n=54; WMD=-8.30; 95% CI, -13.14 to –3.47).

There is limited evidence suggesting that there is a clinically significant difference favouring CBT over wait-list control on improving the likelihood of achieving remission as measured by the HRSD (N=1; n=24; RR=0.45; 95% CI, 0.23 to 0.91).

There is insufficient evidence to determine if there is a clinically significant difference between CBT and wait-list control on improving the likelihood of achieving remission as measured by the BDI (N=1; n=24; RR=0.70; 95% CI, 0.41 to 1.20).

Tolerability and acceptability of treatment

There is no data on which to assess the Acceptability of CBT versus wait-list control.

[3] All statements are from level 1 evidence. The full list of all evidence statements generated from meta-analyses are in Appendix 20; the forest plots are in Appendix 19.

6.2.4.2 Individual CBT compared with pill placebo (plus clinical management)

Data from only one study (ELKIN1989) were available for this comparison. Efficacy data from the other study (JARRETT1999) comparing CBT with placebo plus clinical management were not extracted because more than 50% of the placebo plus clinical management group left the study early.

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and placebo plus clinical management either on increasing the likelihood of achieving remission or on reducing depression symptoms by the end of treatment as measured by either the HRSD or the BDI.

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and placebo plus clinical management on reducing the likelihood of leaving treatment early for any reason.

6.2.4.3 Individual CBT compared with other psychotherapies

The available data were sub-divided to make two comparisons of individual CBT with other psychotherapies. The first combined therapies specifically designed for the treatment of depression (i.e., IPT and behaviour therapy), and the second combined non-directive psychotherapies (i.e., brief psychodynamic therapy, gestalt therapy, Hobson's conversational model of psychodynamic interpersonal psychotherapy, and Rogerian counselling).

Effect of treatment on efficacy outcomes

For both sub-comparisons, there is insufficient evidence to determine whether there is a clinically significant difference between CBT and other psychotherapies on either increasing the likelihood of achieving remission or on reducing depression symptoms.

Tolerability and acceptability of treatment

For both sub-comparisons, there is insufficient evidence to determine whether there is a clinically significant difference between CBT and other psychotherapies on reducing the likelihood of leaving treatment early for any reason.

6.2.4.4 Individual CBT compared with GP care

From the studies of individual CBT, three compared CBT undertaken in primary care with GP care (SCOTT1992, SCOTT1997[4], FREEMAN). (The HRSD data were not extracted from FREEMAN because more than 50% of the participants in the CBT group were missing from this outcome.)

[4] SCOTT1997 also appears in the comparison of CBT versus antidepressants because all but one of the GP care group took antidepressants.

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between CBT provided in primary care and GP care (with antidepressant treatment) on reducing depression symptoms.

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT provided in primary care and GP care on reducing the likelihood of leaving treatment early for any reason.

6.2.4.5 Group CBT compared with other group therapies

There were few RCTs of sufficient quality to assess group CBT fully. It was not possible to make comparisons with either individual CBT, antidepressants or no active treatment. However, a comparison was possible with other group therapies, including gestalt therapy (BEUTLER1991), mutual support group therapy (BRIGHT1999), 'traditional' psychotherapy (COVI1987), and meditation-relaxation therapy (KLEIN1984).

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring group CBT over other group therapies on increasing the likelihood of achieving remission as measured by the BDI (N = 2; *n* =111; RR = 0.60; 95% CI, 0.46 to 0.79).

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between Group CBT and other treatments on reducing the likelihood of leaving treatment early.

6.2.4.6 CBT compared with antidepressants

As described above, antidepressant drugs in some trials in this comparison were administered within the framework of 'clinical management' (ELKIN1989, HAUTZINGER1996, JARRETT1999, KELLER2000, THOMPSON2001). In MIRANDA2003 participants received weekly telephone calls to assess adverse effects, adherence and treatment effects. In the remaining trials, either this is not mentioned (BLACKBURN1981, SCOTT1992) or participants received non-manualised general support (BLACKBURN1997, MURPHY1984). A sub-analysis of the presence or absence of manualised clinical management was not possible because there were insufficient data in the non-clinical management group to calculate an effect size. Therefore, the complete data set was retained. A sub-analysis by mean baseline severity was also undertaken. Participants in one trial (KELLER2000) had chronic depression.

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between CBT and antidepressants on:

- Reducing depression symptoms by the end of treatment as measured by the BDI (N = 8[5]; *n* = 480; SMD = -0.06; 95% CI, -0.24 to 1) or HRSD (N = N = 10[6]; *n* = 1096; SMD = 0.01; 95% CI, -0.11 to 0.13)

- Increasing the likelihood of achieving remission as measured by the HRSD (N = 5; *n* = 839; RR= 1; 95% CI, 0.91 to 1.10).

A sub-analysis by severity did not indicate any particular advantage for antidepressants over CBT based on severity of depression at baseline:

When analysed by severity, there is evidence suggesting that there is no clinically significant difference between CBT and antidepressants on reducing depression symptoms by the end of treatment:

- In moderate or moderate/severe depression assessed with either the HRSD (N= 5; n= 798; Random effects: SMD= 0; 95% CI, -0.22 to 0.22) or the BDI (N = 3; *n* = 184; SMD = -0.06; 95% CI, -0.35 to 0.23)

- In severe depression assessed with either the HRSD (N= 3; n= 197; SMD= -0.04; 95% CI, -0.32 to 0.24) or the BDI (N= 3; n= 197; SMD= 0; 95% CI, -0.28 to 0.28)

- In severe to very severe depression (HRSD: N= 2; n= 101; SMD= -0.10; 95% CI, -0.49 to 0.30; BDI: N= 2; n= 99; WMD= -1.93; 95% CI, -6.02 to 2.16)

- In chronic depression (but with a moderate level of symptoms) (HRSD: N = 1; n = 436; WMD = 0.20; 95% CI, -1.56 to 1.96).

However, one year after treatment, CBT appears to maintain a reduction in symptoms compared to antidepressants:

- There is some evidence suggesting that there is a clinically significant difference favouring CBT over antidepressants on reducing depression symptoms 12 months after treatment as measured by the HRSD and the BDI

[5] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.
[6] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

(HRSD: N=3[7]; *n* = 137; WMD = -4.00; 95% CI, -6.60 to -1.40; BDI: N=3[8]; *n* = 134; WMD = -5.21; 95% CI, -9.37 to -1.04).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and antidepressants on reducing the likelihood of relapse.

Tolerability and acceptability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring CBT over antidepressants on reducing the likelihood of leaving treatment early (N= 10[9]; n= 1042; RR= 0.82; 95% CI, 0.67 to 1).

A sub-analysis showed that this result was mainly due to those with severe to very severe depression:

There is some evidence suggesting that there is a clinically significant difference favouring CBT over antidepressants on reducing the likelihood of leaving treatment early for any reason in people with severe to very severe depression (N= 2; n= 129; RR= 0.41; 95% CI, 0.19 to 0.89).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and antidepressants on reducing the likelihood of leaving treatment early for any reason in people with moderate, moderate/severe depression or severe depression.

6.2.4.7 CBT combined with antidepressants compared with antidepressants alone

Effect of treatment on efficacy outcomes

CBT improves the effect of antidepressants compared to antidepressants alone, although it is not clear if this effect is maintained after treatment:

There is strong evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone (with/without clinical management) on reducing depression symptoms at the end of treatment as measured by the HRSD (N=6; *n* = 724; SMD= -0.46; 95% CI, -0.61 to -0.31).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants over antidepressants alone (with/without

[7] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.
[8] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.
[9] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

clinical management) on increasing the likelihood of achieving remission as measured by the HRSD (N = 4; n = 646; Random effects: RR = 0.76; 95% CI, 0.55 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference between CBT plus antidepressants compared with antidepressants alone (without clinical management) on reducing depression symptoms:

- After 6 months' maintenance treatment as measured by the HRSD and the BDI (HRSD: N = 1; *n* = 16; WMD = 1.70; 95% CI, -1.43 to 4.83; BDI: N = 1; *n* =15; WMD = 2.10; 95% CI, -3.94 to 8.14)

- One year after treatment as measured by the BDI (N = 2; *n* = 92; WMD = -3.78; 95% CI, -8.89 to 1.33).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT combined with antidepressants and antidepressants alone on relapse rates.

The effectiveness of CBT plus antidepressants over antidepressants alone was particularly marked for those with moderate and moderate/severe depression or severe/very severe depression:

There is strong evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone on increasing the likelihood of achieving remission in people with moderate and moderate/severe depression by the end of treatment as measured by the HRSD (N= 2; *n* = 499; RR = 0.71; 95% CI, 0.62 to 0.82).

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD:

- In people with chronic depression (but a moderate level of symptoms) (N = 1; *n* = 454; RR = 0.73; 95% CI, 0.62 to 0.84)

- In people with severe to very severe depression by the end of treatment (N = 1; *n* = 31; RR = 0.47; 95% CI, 0.22 to 0.99).

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone on reducing depression symptoms by the end of treatment:

- In those with moderate or moderate/severe depression as measured by the HRSD (N = 3; *n* = 561; SMD = -0.50; 95% CI, -0.67 to -0.33);

- In those with severe or very severe depression as measured by the BDI (N = 3; *n* = 128; WMD = -4.54; 95% CI, -8.35 to -0.72).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants and antidepressants alone on reducing depression symptoms in those with severe depression one year after treatment (N = 2; *n* = 92; WMD = -3.78; 95% CI, -8.89 to 1.33).

Tolerability and acceptability of treatment

Although it was not possible to detect a statistically significant difference between CBT plus antidepressants and antidepressants alone on the number of participants leaving treatment early for any reason, there was a trend favouring combination treatment:

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants when compared to antidepressants (with/without CM) on reducing the likelihood of leaving treatment early for any reason (N = 8; *n* = 831; RR = 0.81; 95% CI, 0.65 to 1.01).

6.2.4.8 CBT combined with antidepressants compared with CBT alone

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between CBT plus antidepressants and CBT alone on reducing depression symptoms at the end of treatment as measured by the HRSD (N = 4; *n* = 220; WMD = -0.33; 95% CI, -2.07 to 1.40).

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants and CBT alone on reducing the likelihood of leaving treatment early for any reason (N = 5; *n* = 710; RR = 1; 95% CI, 0.77 to 1.30).

6.2.4.9 CBT in residual depression

Two studies looked at the effect of CBT on people with residual symptoms (FAVA1994, PAYKEL1999). The former compared CBT with clinical management and reported relapse data only, and the latter combined CBT with antidepressants and compared this to antidepressants (with clinical management).

The effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between CBT plus antidepressants and antidepressants (with clinical management) in people with residual depression on reducing depression symptoms 17 months after the end of treatment, as measured by the HRSD (*n* = 158; WMD = 0.00; 95% CI, -1.56 to 1.56).

There is evidence suggesting that there is no clinically significant difference between CBT +ADs and ADs (with clinical management) in people with residual depression on reducing depression symptoms at the end of treatment as measured by the HRSD (HRSD: N=1; *n* =158; WMD = -0.70; 95% CI, -2.34 to 0.94).

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants (with clinical management) in people with residual depression on relapse rates 1 year (*n* = 158; RR = 0.60; 95% CI, 0.37 to 0.96; 95% CI, 4 to 50) and 18 months (*n* =158; RR = 0.61; 95% CI, 0.40 to 0.92) after treatment (with continuation treatment).

One study (FAVA1994) followed participants up for 6 years. However, there is insufficient evidence to determine if there is a clinically significant difference between CBT and clinical management in people with residual depression on relapse rates 2 and 6 years after treatment.

There is some evidence suggesting that there is a clinically significant difference favouring CBT over clinical management in people with residual depression on relapse rates 4 years after treatment (N = 1; *n* = 40 ; RR = 0.50; 95% CI, 0.26 to 0.97).

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and other treatments for patients with residual symptoms on reducing the likelihood of leaving treatment early for any reason.

6.2.4.10 Mindfulness-based group CBT as maintenance treatment in treatment responders

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring group mindfulness-based CBT plus usual GP care over usual GP care on reducing the likelihood of reducing relapse 60 weeks after the start of treatment (N= 2; n= 220; RR= 0.74; 95% CI, 0.57 to 0.96).

In people who have had up to two episodes of depression, there is insufficient evidence to determine whether there is a clinically significant difference between mindfulness-based CBT plus usual GP care and usual GP care on reducing the likelihood of reducing relapse 60 weeks after the start of treatment (N= 2; n= 94; RR= 1.42; 95% CI, 0.87 to 2.32).

In people who have had more than two episodes of depression, there is strong evidence suggesting that there is a clinically significant difference favouring group mindfulness-based CBT plus usual GP care over usual GP care on reducing the likelihood of reducing relapse 60 weeks after the start of treatment (N= 2; n= 124; RR= 0.46; 95% CI, 0.29 to 0.72).

6.2.5 Overall clinical summary for CBT

In the only comparison available from a single trial there was insufficient evidence to determine the efficacy of individual CBT for depression compared to either pill placebo (plus clinical management) or other psychotherapies. However stronger data does exist when CBT is compared to antidepressants (a number of which include clinical management), here individual CBT is as effective as antidepressants in reducing depression symptoms by the end of treatment. These effects are maintained a year after treatment in those treated with CBT whereas this may not be the case in those treated with antidepressants. CBT appears to be better tolerated than antidepressants, particularly in patients with severe to very severe depression. There is a trend suggesting that CBT is more effective than antidepressants on achieving remission in moderate depression, but not for severe depression. There was also evidence of greater maintenance of a benefit of treatment for CBT compared to antidepressants. We recognise that this is a different finding to that of Elkin et al (1989).

Adding CBT to antidepressants is more effective than treatment with antidepressants alone, particularly in those with severe symptoms There is no evidence that adding an antidepressant to CBT is generally helpful, although we have not explored effects on specific symptoms (e.g., sleep). The implication of this is whether a patient should have the choice, in the case of severe depression, to receive CBT alone. Level of symptoms will not be the only consideration in offering or making this choice . There is insufficient evidence to assess the effect of CBT plus antidepressants on relapse rates.

There is evidence from one large trial (Keller 2000) that for chronic depression that a combination of CBT and antidepressants is more beneficial in terms of remission than either CBT or antidepressants alone. In residual depression the addition of CBT may also improve outcomes.

It appears to be worthwhile adding CBT to antidepressants compared to antidepressants alone for patients with residual depression as this reduces relapse rates at follow-up, although the advantage is not apparent post treatment.

In regard to modes of delivery there is evidence that group CBT is more effective than other group therapies, but little data on how group CBT fares in comparison to individual CBT. Much may depend on patient preferences for different modes of therapy. However, group mindfulness-based CBT appears to be effective in maintaining response in people who have recovered from depression, particularly in those who have had more than two previous episodes.

6.3 Behaviour therapy (BT)

6.3.1 Introduction

Behaviour therapy for depression evolved from learning theory that posits two types of learning: operant or instrumental learning and classical conditioning. Although classical conditioning theories for depression have been put forward (e.g., Wolpe, 1971; Ferester, 1973) with treatment recommendations (Wolpe, 1979) there has been no treatment trials of this approach. Operant or instrumental learning posits that people acquire depressive behaviours due to the punishment and reinforcers contingent on behaviour. In this approach depression is seen as the result of a low rate of positive rewarded and rewardable behaviour. Hence the therapy focuses on behavioural activation aimed at encouraging the patient to develop more rewarding and task-focused behaviours. The approach was developed by Lewinsohn (1975). In recent years there has been renewed interest in behavioural activation as a therapy in its own right. These therapies include many of the key features earlier behavioural models, such as teaching relaxation skills, problem-solving, engaging in pleasant activities, but also include elements of learning to tolerate and accept certain feelings and situations. Early indications are that behavioural activation has some promise as a treatment for some types of depression (Hopko et al., , 2003)

Definition
Behaviour therapy was defined as a discrete, time limited, structured psychological intervention, derived from the behavioural model of affective disorders and where:

1. Therapist and patient work collaboratively to identify the effects of behaviours on current symptoms, feelings states and/or problem areas.
2. Seek to reduce symptoms and problematic behaviours through behavioural tasks related to: reducing avoidance, graded exposure, activity scheduling, behavioural activation and increasing positive behaviours.

6.3.2 Studies considered for review

No suitable existing systematic review was available. Of the seven references downloaded from searches of electronic databases which appeared to be relevant RCTs, two eventually satisfied the inclusion criteria set by the GDG (GALLAGHER1983 and MCLEAN1979), with five being excluded. No additional trials were found from other sources, including searches of reference lists.

6.3.3 Study characteristics

GALLAGHER1983 12-week RCT (16 sessions) using outpatients referred from regional health centres or private physicians, or self-referred. Mean age of participants 66-69 years.

MCLEAN1979 10-week RCT (8 to 12 sessions) with outpatients meeting Feighner et al (1972) criteria for depression and a BDI of at least 23, with a mean age 39.2 years (+-10.9).

6.3.4 Evidence statements[10]

There is insufficient evidence to determine whether there is a clinically significant difference between behaviour therapy and other psychotherapies on reducing the likelihood of leaving treatment early for any reason.

There is no evidence to determine whether there is a clinically significant difference between behaviour therapy and other psychotherapies on any efficacy outcome.

6.4 Interpersonal Psychotherapy (IPT)

6.4.1 Introduction

Interpersonal Psychotherapy (IPT) was developed by Klerman and Weissman (Klerman et al., 1984) initially for depression although it has now been extended to other areas (Weissman et al., 2000). IPT focuses on current relationships, not past ones and on interpersonal processes rather than intrapsychic ones (such as negative core beliefs or automatic thoughts as in CBT, or unconscious conflicts as in psychodynamic therapy). It is time limited and focused on difficulties arising in the daily experience of maintaining relationships and resolving difficulties whilst suffering an episode of major depression. The main clinical tasks are to help patients to learn to link their mood with their interpersonal contacts and to recognise that, by appropriately addressing interpersonal situations, they may simultaneously improve both their relationships and their depressive state. Early in the treatment patient and therapist agree to work on a particular focal area that would include, interpersonal role transitions, interpersonal roles/conflicts, grief and/or interpersonal deficits. For people to be appropriate for IPT they will need to have a key appropriate focus area. IPT can be delivered as an individual focused therapy but has also been developed as a group therapy (Wilfley et al., 2000). (ibid.).

The character of the therapy sessions is largely , facilitating understanding of recent events in interpersonal terms and exploring alternative ways of handling interpersonal situations. Although there is not an explicit emphasis on "homework" tasks may be done between sessions.

[10] The full list of all evidence statements generated from meta-analyses (and the associated forest plots) will be available on the CD-ROM that accompanies the guideline.

6.4.2 Definition

Interpersonal therapy was defined as a discrete, time limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and where:

1. Therapist and patient work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems.
2. Seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

6.4.3 Studies considered for review

No suitable existing systematic review was available. Of the 107 references downloaded from searches of electronic databases, 16 appeared to be relevant RCTs, with 8 eventually satisfying the inclusion criteria set by the GDG, and 8 being excluded. No additional trials were found from other sources, including searches of reference lists.

6.4.4 Study characteristics

The eight included studies looked at IPT in a variety of settings, including outpatient and primary care. Most were undertaken in the US, although one (DELMELLO2001) was Brazilian and another (FREEMAN) is British. Two studies looked at older adults, and in one, most participants were diagnosed with double depression (i.e., dysthymia superimposed on major depressive disorder) (DEMELLO2001) rather than major depression alone. Two studies looked at IPT during a continuation phase after successful acute phase treatment (REYNOLDS1999, SCHULBERG1996), and two examined IPT during a 3-year maintenance treatment in treatment responders (FRANK1990, REYNOLDS1999B).

6.4.5 Evidence statements

6.4.5.1 IPT compared with placebo (plus clinical management) or usual GP care

Effect of treatment on efficacy outcomes

IPT is more effective than either placebo plus clinical management or usual GP care. In both studies comparing IPT with usual GP care, patients receiving GP care were prescribed antidepressants: in SCHULBERG1996 45%, and in FREEMAN all patients.

There is some evidence suggesting that there is a clinically significant difference favouring IPT over placebo plus clinical management on:

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; n = 123; WMD = -3.4; 95% C.I., -6.17 to -0.63)

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; n = 123; RR = 0.73; 95% C.I., 0.56 to 0.93).

There is some evidence suggesting that there is a clinically significant difference favouring IPT over usual GP care on reducing depression symptoms by the end of treatment as measured by the BDI and HRSD (BDI: N = 1; n = 72; WMD = -9.23; 95% C.I., -15.45 to -3.01; HRSD: N = 1; n = 185; WMD = -3.09; 95% C.I., -5.59 to -0.59).

Tolerability and acceptability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring usual GP care over IPT on reducing the likelihood of leaving treatment early (N = 1; n = 185; RR = 4.14; 95% C.I., 2.29 to 7.47).

There is some evidence suggesting that there is a clinically significant difference favouring IPT over placebo plus clinical management on reducing the likelihood of leaving treatment early for any reason (N = 1; n = 123; RR = 0.57; 95% C.I., 0.33 to 0.99).

6.4.5.2 IPT combined with antidepressants

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over IPT alone (with/without placebo) on achieving remission by the end of treatment as measured by the HRSD (N = 1; n = 33; RR = 2.26; 95% C.I., 1.03 to 4.97).

However, there was insufficient evidence to assess IPT in combination with antidepressants compared with antidepressants alone.

Tolerability and acceptability of treatment

- There was insufficient evidence to determine whether IPT was more acceptable than any comparator treatment for which data was available.

6.4.5.3 IPT as a continuation treatment

Effect of treatment on efficacy outcomes

When used as continuation treatment after response and in comparison with treatment as usual (TAU), IPT was effective in the treatment of depression:

There is some evidence suggesting that, after 4 months' continuation treatment, there is a clinically significant difference favouring IPT over TAU on:

- increasing the likelihood of achieving remission as measured by the HRSD (N = 1; n = 185; RR = 0.66; 95% C.I., 0.53 to 0.82)

- reducing depression symptoms as measured by the HRSD (N = 1; n = 185; WMD = -3.8; 95% C.I., -6.29 to -1.31).

However, there is insufficient evidence to determine efficacy against antidepressants, either alone or in combination with antidepressants.

There is strong evidence suggesting that, after three years' maintenance treatment, there is a clinically significant difference favouring IPT plus antidepressants over:

- IPT plus placebo on relapse rates (N = 2; n = 101; RR = 0.42; 95% C.I., 0.27 to 0.65)

- medication clinic plus placebo on relapse rates (N = 1; n = 54; RR = 0.22; 95% C.I., 0.1 to 0.49).

There is some evidence suggesting that, after three years' maintenance treatment, there is a clinically significant difference favour IPT plus antidepressants over IPT alone on relapse rates (N = 1, n = 51; RR = 1.73; 95% CI, 1 to 2.98).

There is some evidence suggesting that, after three years' maintenance treatment, there is a clinically significant difference favouring IPT plus placebo over medication clinic plus placebo on relapse rates (N = 2; n = 103; RR = 0.8; 95% C.I., 0.66 to 0.97).

- There was insufficient evidence to determine the efficacy of IPT against other comparator treatments for which data was available.

Tolerability and acceptability of treatment

There are no data on which to assess the tolerability and acceptability of IPT as a continuation treatment.

6.4.6 Clinical summary

IPT has been the subject of a small number of well-designed RCTs. There is some evidence to suggest that IPT is more effective than placebo and usual GP care and that its effectiveness may be increased when combined with an antidepressant. There was insufficient evidence to compare IPT with other psychological interventions (see section 6.2 on CBT). It can also be effective as a maintenance intervention where patients have remitted following previous treatment. Studies of long-term relapse prevention are yet to be conducted.

6.5 Problem-Solving Therapy

6.5.1 Introduction

It has long been recognised that depression is associated with social problem solving difficulties (Nezu, 1987). The reasons for this may be various, relating to the effects of depressed state, lack of knowledge, and rumination. As a consequence, helping patients solve problems and develop problem solving skills has been a focus for therapeutic intervention and development of therapy (Nezu, Nezu & Perri, 1989). There has been recent interest in developing problem solving therapies for use in primary care (Barrett et al., 1999).

6.5.2 Definition

Problem-solving therapy was defined as a discrete, time limited, structured psychological intervention, that focuses on learning to cope with specific problems areas and where:

- Therapist and patient work collaboratively to identify and prioritise key problem areas, to break problems down into specific, manageable tasks, problem solve, and develop appropriate coping behaviours for problems.

6.5.3 Studies considered for review

6.5.3.1 Source of studies

No suitable existing systematic review was available. Of the 188 references downloaded from searches of electronic databases, 11 appeared to be relevant RCTs, with 3 eventually satisfying the inclusion criteria set by the GDG, and 8 being excluded. No additional trials were found from other sources, including searches of reference lists.

6.5.3.2 Study characteristics

The two included studies were:

- DOWRICK2000 – patients responding to a survey, all met DMS-IV criteria for major depressive disorder (single episode or recurrent), dysthymia (16%), adjustment disorder (4%) or other (9%). Baseline BDI around 22 points. Nine-centre international trial comparing no treatment with either problem-solving therapy or group psychoeducation. Problem-solving therapy versus no treatment control is extracted for this section.
- MYNORS-WALLIS1995 – patients from primary care, all met RDC criteria for major depression, with an HRSD score over 13; problem-solving therapy is compared with pharmacotherapy (amitriptyline at 150 mg /day) and pill placebo.
- MYNORS-WALLIS2000 – patients from primary care, meeting RDC criteria for probable or definite major depression, with an HRSD score over 13; problem-solving therapy (either by a GP or practice nurse) is compared with

pharmacotherapy (fluvoxamine (100-150 mg) or paroxetine (10-40mg) and with a combination of psychotherapy and pharmacotherapy.

All gave participants six sessions over a period of three months.

6.5.4 Evidence statements

6.5.4.1 Problem-solving versus placebo or no treatment control

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring problem solving over placebo on:

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; n = 55; WMD = -4.7; 95% C.I., -8.42 to -0.98) and BDI (N = 1; n = 55; WMD = -7.8; 95% C.I., -13.78 to -1.82)

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; n = 60; RR = 0.55; 95% C.I., 0.33 to 0.89) and BDI (N = 1; n = 60; RR = 0.62; 95% C.I., 0.39 to 0.99).

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving and no treatment on increasing the likelihood of not being diagnosed with a depressive disorder:

- 6 months after the start of treatment (N = 1; n = 245; RR = 0.83; 95% C.I., 0.68 to 1.02)

- 12 months after the start of treatment (N = 1; n = 245; RR = 0.98; 95% C.I., 0.79 to 1.22).

Tolerability and acceptability of problem-solving therapy

There is strong evidence suggesting that there is a clinically significant difference favouring problem-solving over placebo on reducing the likelihood of leaving treatment early for any reason (N = 1; n = 60; RR = 0.11; 95% C.I., 0.03 to 0.44).

There is insufficient evidence to determine whether there is a clinically significant difference between problem solving and placebo on increasing the likelihood of leaving treatment early due to side-effects (N = 1; n = 60; RR = 0.2; 95% C.I., 0.01 to 4).

6.5.4.2 Problem-solving versus antidepressants

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between problem solving and antidepressants when compared to antidepressants alone on any efficacy measure:

- Increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; n = 116; RR = 1.43; 95% C.I., 0.85 to 2.39)) or BDI (N = 1; n = 61; RR = 0.67; 95% C.I., 0.41 to 1.09)

- Reducing depression symptoms by the end of treatment as measured by the HRSD or BDI (HRSD: N = 2; n = 124; WMD = 0.65; 95% C.I., -1.9 to 3.21; BDI: N = 2; n = 124; WMD = -1.34; 95% C.I., -5.23 to 2.55).

One year after the end of treatment there is insufficient evidence to determine whether there is a clinically significant difference between problem solving and antidepressants on:

- increasing the likelihood of achieving remission as measured by the HRSD (N = 1; n = 116; RR = 0.93; 95% C.I., 0.59 to 1.45)

- reducing depression symptoms one year after the end of treatment as measured by the HRSD (N = 1; n = 55; WMD = -1.4; 95% C.I., -5 to 2.2) or BDI (N = 1; n = 55; WMD = -1.9; 95% C.I., -8.83 to 5.03).

Tolerability and acceptability of problem-solving therapy

There is insufficient evidence to determine whether there is a clinically significant difference between problem solving and antidepressants on increasing the likelihood of leaving treatment early for any reason (N = 2; n = 177; Random Effects RR = 0.88; 95% C.I., 0.18 to 4.2).

There is some evidence suggesting that there is a clinically significant difference favouring problem-solving over antidepressants on increasing the likelihood of leaving treatment early due to side-effects. (N = 2; n = 177; RR = 0.12; 95% C.I., 0.01 to 0.97).

6.5.4.3 Problem-solving plus antidepressants versus antidepressants alone

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between problem solving and antidepressants when compared to antidepressants alone on any efficacy measure:

- Increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD N = 1; n = 71; RR = 1.2; 95% C.I., 0.65 to 2.22)

- Reducing depression symptoms by the end of treatment as measured by the HRSD or BDI (HRSD: N = 1; n = 65; WMD = 1.3; 95% C.I., -2.09 to 4.69; BDI: N = 1; n = 65; WMD = -2.5; 95% C.I., -7.33 to 2.33).

One year after the end of treatment there is insufficient evidence to determine whether there is a clinically significant difference between problem solving and antidepressants v antidepressants on:

- increasing the likelihood of achieving remission as measured by the HRSD. (N = 1; n = 71; RR = 0.77; 95% C.I., 0.43 to 1.39)
- on maintaining a reduction in depression symptoms as measured by the HRSD (N = 1; n = 60; WMD = -1.5; 95% C.I., -4.47 to 1.47) or BDI (N = 1; n = 60; WMD = -2.9; 95% C.I., -8.64 to 2.84).

Tolerability and acceptability of problem-solving therapy

There is insufficient evidence to determine whether there is a clinically significant difference:

- between problem solving and AD v AD on reducing the likelihood of leaving treatment early for any reason (N = 1; n = 71; RR = 1.03; 95% C.I., 0.37 to 2.89);

- between problem solving and AD v AD on reducing the likelihood of leaving treatment early due to side effects (N = 1; n = 71; RR = 2.06; 95% C.I., 0.4 to 10.52).

6.5.4.4 Problem-solving administered by a GP compared to problem-solving administered by a nurse

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving therapy administered by a GP and problem-solving therapy administered by a nurse on reducing depression symptoms by the end of treatment as measured by the HRSD or BDI (HRSD: N = 1; n = 70; WMD = -0.2; 95% C.I., -3.95 to 3.55; BDI: N = 1; n = 70; WMD = -0.8; 95% C.I., -6.25 to 4.65).

6.5.5 Clinical summary

Problem solving provides direct and practical support for patients with mild depression with their current life difficulties. The evidence is that this can be helpful for patients with mild depression and may be as useful to them as antidepressants. Both appropriately trained GPs and practice nurses can deliver this treatment effectively. However, all the studies of problem-solving therapy have been carried out in primary care; we do not know about its value in secondary care (for example, how it compares with active drugs or with CBT) and for depression other than in its mild form.

6.6 Counselling

6.6.1 Introduction

Counselling was developed by Carl Rogers (1957) who believed that people had the means for self-healing, problem resolution and growth if the right conditions could be created. These include the provision of positive regard, genuineness and empathy. Roger's original model was developed into structured counselling approaches by Truax and Carkhuff (1967) and, independently, by Egan (e.g., 1990) who developed the three stage model: exploration, personalising and action. Voluntary sector counselling training (e.g. Relate) tends to draw on these models. Counsellors are taught to listen and reflect patient feelings and meaning (Rogers, 1957). Although many other therapies now use these basic ingredients of client-centred counselling (Roth & Fonagy, 1996) there are differences in how they are used (Kahn, 1985; Rogers, 1986). Today, however, counselling is really a generic term used to described a broad range of interventions delivered by counsellors usually working in primary care; the various of approaches may include psychodynamic, systemic or cognitive behavioural (Bower et al., 2003).

The British Association for Counselling and Psychotherapy define counselling in terms of "active listening", where "…. the client can explore various aspects of their life and feelings, talking about them freely and openly in a way that is rarely possible with friends and family. Bottled up feelings such as anger, anxiety, grief and embarrassment can become very intense and counselling offers an opportunity to explore them with a possibility of making them easier to understand. The counsellor will encourage the expression of feelings and as a result of their training will be able to accept and reflect the client's problems without becoming burdened by them".

6.6.2 Definition

For the guideline counselling was defined as a discrete, usually time limited, psychological intervention where:

1. The intervention may have a facilitative approach often with a strong focus on the therapeutic relationship but may also be structured and at times directive
2. An intervention was classified as counselling if the intervention(s) offered in the study did not fulfil all the criteria for any other psychological intervention. If a study using counsellors identifies a single approach, such as cognitive behavioural or interpersonal, it has been analysed in that category.

6.6.3 Source of studies

No suitable existing systematic review was available. Of the 1,027 references downloaded from searches of electronic databases, nine appeared to be relevant RCTs, with three eventually satisfying the inclusion criteria set by the GDG, and 6 being excluded. No additional trials were found from other sources, including searches of reference lists.

6.6.3.1 Study characteristics

The three included studies were BEDI2000, SIMPSON2003 and WARD2000, all of which were carried out in the UK.

- BEDI2000 studied outpatients recruited via GP practices with a diagnosis of major depression (RDC) and a mean baseline BDI of around 27 (+-8). The comparator treatment was antidepressant medication. GPs had a choice of three drugs which had to be given at an adequate dose for between 4 and 6 months after response. Counsellors used whatever approach they felt was most appropriate.
- SIMPSON2003 studied participants from primary care with a BDI score of at least 14 and had been depressed for at least six months – many patients on concurrent medication during the trial. Counsellors followed a psychodynamic Freudian model.
- WARD2000 studied GP referrals with a BDI score of at least 14, although depression was the primary diagnosis in only 62% of the sample. The comparator treatments were CBT and 'usual GP care'. Due to the problem with diagnosis, this trial was excluded from the review of CBT. However, it is included here because of the lack of suitable trials. In addition, despite GPs being asked not prescribe antidepressants for study patients receiving psychotherapy, 30% of the counselling group and 27% of those receiving CBT took concomitant antidepressants. Counsellors used a non-directive approach.

6.6.4 Evidence statements

Effect of treatment on efficacy outcomes

When compared to GP care, counselling appears to be effective, although there is insufficient evidence at follow-up:

There is some evidence suggesting that there is a clinically significant difference favouring counselling over GP care on reducing depression symptoms at the end of treatment as measured by the BDI (N = 1; n = 134; WMD = -5.4; 95% C.I., -9.11 to -1.69).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and GP care on reducing depression symptoms 12 months after treatment as measured by the BDI (N = 1; n = 134; WMD = -0.3; 95% C.I., -3.67 to 3.07).

When compared with antidepressants, counselling appears to help achieve remission at follow-up, although only one study made this comparison (BEDI2000):

There is some evidence suggesting that there is a clinically significant difference favouring antidepressants over counselling on increasing the likelihood of achieving remission 12 months after the end of treatment as measured by the RDC (N = 1; n = 103; RR = 1.41; 95% C.I., 1.08 to 1.83).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and antidepressants on maintaining a reduction in depression symptoms 12 months after the end of treatment as measured by the BDI (N = 1; n = 65; WMD = 2.1; 95% C.I., -3.88 to 8.08).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and CBT on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; n = 130; WMD = -1.4; 95% C.I., -4.87 to 2.07);

- reducing depression symptoms twelve months after the end of treatment as measured by the BDI (N = 1; n = 130; WMD = 0.4; 95% C.I., -3.12 to 3.92).

When added to GP care and compared with GP care alone there is no advantage in patients who have been depressed for at least six months:

There is evidence suggesting that there is no clinically significant difference between counselling plus GP care and GP care alone on reducing depression symptoms six months after the start of treatment to below 14 points on the BDI (N = 1; n = 145; RR = 0.94; 95% C.I., 0.73 to 1.22).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling plus GP care and GP care alone on any other outcome including at follow up.

Tolerability and acceptability of treatment

There was no evidence for tolerability against antidepressants or CBT. However, when compared to GP care:

There is some evidence suggesting that there is a clinically significant difference favouring counselling over GP care on reducing depression symptoms at the end of treatment as measured by the BDI. (N = 1; n = 134; WMD = -5.4; 95% C.I., -9.11 to -1.69)

There is insufficient evidence to determine whether there is a clinically significant difference between counselling plus GP care and GP care alone on reducing the likelihood of patients leaving the study early (N = 1; n = 145; RR = 1.13; 95% C.I., 0.43 to 2.95).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and CBT on leaving the study early four months after the start of treatment (N = 1; n = 130; RR = 0.67; 95% C.I., 0.22 to 2.01).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and CBT on leaving the study early twelve months after the start of treatment (N = 1; n = 130; RR = 0.65; 95% C.I., 0.3 to 1.42).

6.6.5 Clinical summary

Counselling as currently delivered in the NHS covers a wide range of different interventions, to some extent that variety in the nature of the intervention was reflected in the studies reported here. There is evidence for the efficacy of counselling for depression in primary care for patients with mild to moderate depression of recent onset when it is compared with antidepressants, GP care and other psychological interventions. There is no evidence of its effectiveness for chronic depression. The evidence reviewed here favours the use of brief, pragmatic structured approaches to counselling in primary care although it appears to be effective. There was little evidence about tolerability. Adding counselling to GP care does not add any particular advantages in those with chronic depression.

6.7 Short-term psychodynamic psychotherapy

6.7.1 Introduction

Psychodynamic psychotherapy is a derivative of psychoanalysis. As with other schools of therapy there are now a variety of variations and hybrids of the original model with some approaches focusing on the dynamic of drives (e.g., aggression) while others focus on relationships (Greenberg & Mitchell, 1983). Other forms of this type of therapy have been influenced by attachment theory (Holmes, 2001). Clinical trials of psychodynamic psychotherapy have focused on short-term psych therapy (10-20 weeks) usually in comparison with antidepressants, CBT or BT.

6.7.2 Definition

Psychodynamic interventions were defined as , psychological interventions, derived from a psychodynamic/psychoanalytic model and where:

1. Therapist and patient explore and gain insight into conflicts and how these are represented in current situations and relationships including the therapy relationship (e.g., transference and counter-transference).

2. This leads to patients being given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, and the technical focus is on interpreting and working though conflicts.
3. Therapy is non-directive and recipients are not taught specific skills (e.g., thought monitoring, re-evaluating, or problem solving).

6.7.3 Studies considered for review

6.7.3.1 Source of studies

No suitable existing systematic review was available. Of the 188 references downloaded from searches of electronic databases, 10 appeared to be relevant RCTs, with three eventually satisfying the inclusion criteria set by the GDG (GALLAGHER-THOMPSON1994, MCLEAN1979, SHAPIRO1994), and 8 being excluded. An additional trial (BURNAND2002) was sourced through an update search undertaken towards the end of the guideline development process. No further trials were found from other sources, including searches of reference lists.

6.7.3.2 Study characteristics

BURNAND2002 – participants were referred to acute outpatient treatment at a community mental health centre. All had major depressive disorder according to DSM-IV criteria and HRSD >= 20 at baseline. The trial compared psychodynamic psychotherapy plus clomipramine with clomipramine and supportive therapy (providing empathetic listening, guidance, support and facilitation of an alliance by one carefully designated caregiver). Trial length: 10 weeks; number of sessions not clear.

GALLAGHER-THOMPSON1994 - caregivers recruited through referrals from health care professionals. The majority of participants met RDC criteria for major depression, with the remainder meeting criteria for minor depression. Brief psychodynamic therapy is compared with CBT. Trial length: 16-20 sessions, twice a week for first 4 weeks, then once a week for remainder of therapy (?c20 weeks)

MCLEAN1979 - participants were outpatients meeting Feighner et al (1972) criteria for depression and a BDI score of at least 23. This was a three-arm trial comparing psychodynamic psychotherapy with behaviour therapy and antidepressants. Efficacy data were not extracted because dropouts were replaced. Trial length: 10 sessions over 10 weeks.

SHAPIRO1994 – participants were outpatients recruited from self-referrers responding to recommendations by occupational health personnel or responding to publicity materials distributed at the workplace or by GPs, or referred directly by GPs or mental health services. All had a diagnosis of major depressive disorder (DSM-III). Psychodynamic-interpersonal psychotherapy based on Hobson's conversational model is compared with CBT. Trial length: 16 weeks.

6.7.4 Evidence statements

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy and CBT on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 3; n = 57; WMD = 3.21; 95% C.I., 0.11 to 6.32)
- reducing depression symptoms by 6 months after treatment as measured by the BDI (N = 3; n = 56; WMD = 1.44; 95% C.I., -2.7 to 5.58)
- reducing depression symptoms by one year after treatment as measured by the BDI (N = 3; n = 50; WMD = -1.2; 95% C.I., -4.96 to 2.57)
- reducing the likelihood of still being depressed at the end of treatment as measured by RDC criteria (N = 1; n = 66; RR = 1.7; 95% C.I., 0.97 to 2.97)
- reducing the likelihood of still being depressed three months after treatment as measured by RDC criteria (N = 1; n = 66; RR = 1.34; 95% C.I., 0.86 to 2.08).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy plus antidepressants and antidepressants plus supportive therapy on

- increasing the likelihood of achieving remission by the end of treatment (N = 1; n = 95; RR = 1.09; 95% C.I., 0.8 to 1.48)
- reducing depression symptoms by the end of treatment (N = 1; n = 74; WMD = -0.8; 95% C.I., -4.06 to 2.46).

Effect of treatment on tolerability

There is some evidence suggesting that there is a clinically significant difference favouring behaviour therapy over psychodynamic therapy on reducing the likelihood of leaving treatment early (N = 1; n = 95; RR = 3.02; 95% C.I., 1.07 to 8.5).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic treatment and antidepressants on reducing the likelihood of leaving treatment early (N = 1; n = 90; RR = 0.76; 95% C.I., 0.41 to 1.41).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy and CBT on reducing the likelihood of leaving treatment early (N = 1; n = 66; RR = 2.16; 95% C.I., 0.81 to 5.76).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy plus antidepressants and antidepressants plus supportive therapy on reducing the likelihood of leaving treatment early (N = 1; n = 95; RR = 1.43; 95% C.I., 0.71 to 2.89).

6.7.5 Clinical summary

Despite the fact that psychodynamic psychotherapy is the most established psychotherapy, good quality research studies are rare. Comparisons between short-term psychodynamic therapy and CBT or antidepressants demonstrate a clear but not definitive trend towards increasing effectiveness for drugs and CBT at end of treatment. The potential superior efficacy of antidepressants and CBT is not maintained at follow-up.

6.8 Couple-focused therapies

6.8.1 Introduction

Therapists have noted that a partner's critical behaviour may trigger an episode, and/or maintain or exacerbate relapse in the long term (eg Hooley & Teasdale, 1989), although other researchers have questioned this, e.g., Hayhurst et al. (1997). Couple therapies focus on the way distressed couples differ from non-distressed couples and teach communication and impersonal skills to increase relationship satisfaction (Wheeler et al., 2001). There has also been some work looking at differences in the vulnerabilities between men and women within an intimate relationship, with physical aggression by a partner predicting depression in women. Difficulties in developing intimacy, and coping with conflict, also predict depression in both men and women (Christian et al., 1994). In some forms of therapy depression is seen to constitute a challenge to the relationship and therapy is aimed at coping with the depression. In other forms of therapy the relationship interacts with the depression. Each may be true for different people. Like other therapies this approach has evolved in recent years. For example, Wheeler et al., (2001) have outlined the development of integrative couple behaviour therapy, from traditional cognitive behavioural therapy with an outline of the key therapeutic principals. Systemic couple-therapy aims to give the couple new perspectives on the

presenting problem (e.g. depressing behaviours), and explore new ways of relating (Jones & Aser, 1999). In our analysis of couples therapy, where one partner, is depressed, we have not focused on a specific approach but define couples therapy more generally.

6.8.2 Definition

Couples therapy, was defined as, a time limited, psychological intervention derived from a model of the interactional processes in relationships where:

1. Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of symptoms and problems.
2. The aim is to change the nature of the interactions so that they may develop more supportive and less conflictual relationships.

The style of the therapy can vary and reflect different approaches, e.g., cognitive behavioural or psychodynamic.

6.8.3 Studies considered for review

6.8.3.1 Source of studies

No suitable existing systematic review was available. Of the 42 references downloaded from searches of electronic databases, 15 appeared to be relevant RCTs, with 5 eventually satisfying the inclusion criteria set by the GDG and 10 being excluded. No additional trials were found from other sources, including searches of reference lists.

6.8.3.2 Study characteristics

Participants in the five included studies were couples in which at least one partner met criteria for depression and where marital difficulties had been identified. Three were undertaken in the US (BEACH1992, FOLEY1989, OLEARY1990), one (LEFF2000) in the UK and one in Holland (EMANUELS-ZUUVEEN1996) undertaken in Holland. Most studies used CBT or IPT tailored to couples. LEFF2000, however, used systemic couples therapy.

6.8.4 Evidence statements[11]

Effect of treatment on efficacy

There is strong evidence suggesting that there is a clinically significant difference favouring couples therapy over wait-list control on reducing depression symptoms by the end of treatment as measured by the BDI (N = 2; n = 54; WMD = -11.64; 95% C.I., -16.12 to -7.16).

Unfortunately, there was no evidence to make a comparison with antidepressants, since more than 50% of participants in the antidepressant group in only available study (LEFF2000) left treatment early.

There is insufficient evidence to determine whether there is a clinically significant difference between couples therapy and individual therapy (CBT or IPT) on reducing depression symptoms at the end of treatment as measured by the BDI or HRSD (BDI: N = 2; n = 57; WMD = -2.73; 95% C.I., -7.06 to 1.6; HRSD: N = 1; n = 18; WMD = 0.6; 95% C.I., -11.04 to 12.24).

Tolerability and acceptability of couples therapy

There is some evidence suggesting that there is a clinically significant difference favouring couples therapy over antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 1; n = 77; RR = 0.4; 95% C.I., 0.21 to 0.75).

There is insufficient evidence to determine whether there is a clinically significant difference between couples therapy and antidepressants on reducing the likelihood of leaving treatment early due to side effects (N = 1; n = 77; RR = 0.31; 95% C.I., 0.01 to 7.36).

There is insufficient evidence to determine whether there is a clinically significant difference between couples therapy and individual therapy (CBT or IPT) on reducing the likelihood of leaving treatment early (N = 3; n = 84; RR = 1.22; 95% C.I., 0.56 to 2.65).

6.8.5 Clinical summary

There is some evidence for couples therapy as an effective treatment for depression when compared to wait-list control, and it appeared to be more acceptable than antidepressants. It appears to be as acceptable as individual therapy (CBT and IPT). Unfortunately, there was no evidence to determine its efficacy compared to antidepressants.

6.9 Psychological interventions in older adults

6.9.1 Introduction

It is well known that after the age of 65 there is an increasing risk of major life events associated with depression. These include loss of employment, loss of intimate (e.g. spouse), changing social environments (such as retirement move), increasing risk of social isolation and changes in health status (Tolliver, 1983). Indeed it is estimated that approximately 15% of older adults may be depressed at any one time (Beekman et al., 1999). Depression is a major cause of suicide in older adults (Lebowitz et al., 1997) and depression can significantly handicap people's ability to cope with physical ailments. Depression can often present as pseudo-dementia (Wells – this was 1979/1978 in American Journal of Psychiatry). As most older patients with symptoms of depression will be seen in

primary care, it is important that clinicians consider depressive symptoms in the context of life events and ongoing difficulties. However, attention and one study of reminiscence therapy also showed promise (McCusker, J., Cole, M., Keller, E., Bellavance, F., & Anick, B [1998] Effectiveness of treatments of depression in older ambulatory patients. Archives of Internal Medicine. 158, 705-712).

6.9.2 Studies reviewed

From the studies reviewed elsewhere in this Chapter, four were exclusively of older adults (mean age 65 years or over). Three of these were of IPT (REYNOLDS1999; REYNOLDS1999B; WEISSMAN1992) and one of CBT (THOMPSON2001).

6.9.3 Evidence statements[12]

6.9.3.1 CBT versus antidepressants

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT and antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; n = 64; WMD = -2.20; 95% CI, -6.41 to 2.01)

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; n = 64; WMD = -2.50; 95% CI, -5.75 to 0.75).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT and antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 1; n = 64; RR = 0.62; 95% CI, 0.28 to 1.37).

6.9.3.2 Older patients: CBT plus antidepressants versus antidepressants

Effect of treatment on efficacy

In elderly patients there is insufficient evidence to determine if there is a clinically significant difference between CBT plus antidepressants and antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; n = 69; WMD = -2.90; 95% CI, -6.63 to 0.83)

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; n = 69; WMD = -3.00; 95% CI, -6.09 to 0.09).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT plus antidepressants and antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 1; n = 69; RR = 0.92; 95% CI, 0.48 to 1.75).

6.9.3.3 Older patients: IPT (with/without placebo) versus IPT + antidepressants

Effect of treatment on efficacy

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over IPT (with/without placebo) on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; n = 33; RR = 2.26; 95% CI, 1.03 to 4.97).

Tolerability and acceptability

In older patients there is insufficient evidence to determine whether there is a clinically significant difference between IPT (with/without placebo) and IPT plus antidepressants on:

- leaving treatment early for any reason (N = 2; n = 58; RR = 1.44; 95% C.I., 0.72 to 2.86)
- leaving treatment early due to side-effects (N = 2; n = 58; RR = 0.34; 95% C.I., 0.06 to 2.08).

6.9.3.4 Older patients: IPT plus antidepressants versus antidepressants

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and antidepressants on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; n = 41; RR = 0.71; 95% CI, 0.30 to 1.66).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and antidepressants on:

- reducing the likelihood of leaving treatment early for any reason (N = 1; n = 41; RR = 0.10; 95% CI, 0.01 to 1.67)
- reducing the likelihood of leaving treatment early for any reason (N = 1; n = 41; RR = 0.31; 95% CI, 0.02 to 5.99).

6.9.3.5 IPT (with/without placebo) versus antidepressants (with/without clinical management)

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT and antidepressants on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; n = 42; RR = 1.60; 95% CI, 0.94 to 2.75).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT and antidepressants on:

- reducing the likelihood of leaving treatment early for any reason (N = 1; n = 42; RR = 0.63; 95% CI, 0.19 to 2.10)
- reducing the likelihood of leaving treatment early for any reason (N = 1; n = 42; RR = 0.29; 95% CI, 0.01 to 5.67).

6.9.3.6 IPT as maintenance treatment (3 years)

Effect of treatment on efficacy

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over IPT plus placebo on:

- reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; n = 50; RR = 0.31; 95% CI, 0.14 to 0.72)
- reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; n = 54; RR = 0.22; 95% CI, 0.10 to 0.49).

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus placebo over medication clinic plus placebo on reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; n = 54; RR = 0.71; 95% CI, 0.52 to 0.98).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and medication clinic plus antidepressants on reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; n = 53; RR = 0.47; 95% CI, 0.19 to 1.14).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and IPT plus placebo on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; n = 50; RR = 0.75; 95% CI, 0.19 to 3.01).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and medication clinic plus placebo on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; n = 54; RR = 8.08; 95% CI, 0.44 to 149.20).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus placebo and medication clinic plus placebo on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; n = 54; RR = 10.38; 95% CI, 0.59 to 183.92).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and antidepressants on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; n = 53; RR = 0.84; 95% CI, 0.21 to 3.39).

6.9.4 Clinical summary

There are few RCTs of psychotherapies undertaken on exclusively older populations. Therefore, there is largely insufficient evidence for the efficacy of psychological therapies in this patient group. There is some evidence, however, for the addition of antidepressants to IPT compared to IPT alone on achieving remission by the end of treatment and on reducing the likelihood of relapse after the years' maintenance treatment.

6.9.5 Clinical practice recommendations

6.10 Short-term psychological treatments

6.10.1 Introduction

In primary care, there is a clear desire to find effective and rapid treatments for depression, particularly milder disorders. This has led to the development of short-term cognitive behavioural and other structured psychological therapies with 6 to 8 sessions. Most short-term interventions cover the same material as long-term therapies, but introduce it at a faster rate. In addition, therapists aim to establish a therapeutic relationship with clients much more quickly. Clients are expected to be able to articulate their problems clearly, not to have difficult interpersonal problems that would interfere with the establishing of a good therapeutic alliance, able to understand and appreciate the rationale of the therapy, and able to engage in independent work outside the therapy sessions.

6.10.2 Studies considered for review

the following studies of short-term psychotherapy (6 to 12 sessions) included in other sections of this chapter were used:

BEDI2000 (Counselling versus GP care (including antidepressants))

MIRANDA2003 (CBT v antidepressants)

MYNORS-WALLIS1995 (Problem-solving therapy versus antidepressants versus placebo)

MYNORS-WALLIS2000 (Problem-solving therapy versus antidepressants (versus combination treatment - not used))

SCOTT1997 (CBT v GP care (most participants on antidepressants))

SELMI1990 (CBT v wait list control (versus C-CBT – not used))

SHAPIRO1994 (CBT v psychodynamic psychotherapy)

SIMPSON2003 (Counselling + GP care v GP care (some participants on antidepressants))

WARD2000 (Counselling v GP care (some participants on antidepressants))

Short-term psychological therapy was compared with other treatments and with placebo and wait list control.

6.10.3 Evidence statements

6.10.3.1 Short-term psychotherapies versus other therapies

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on reducing the likelihood of leaving treatment early for any reason (N= 5; n= 504; RR= 1.16; 95% CI, 0.75 to 1.79).

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over other treatments on reducing the likelihood of leaving treatment early due to side effects (N= 2; n= 177; RR= 0.12; 95% CI, 0.01 to 0.97).

Effect of treatment on efficacy outcomes at the end of treatment

There is evidence suggesting that there is a statistically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms by the end of treatment as measured by the BDI, but there

is insufficient evidence to determine its clinical significance (N= 8; n= 481; WMD= -1.89; 95% CI, -3.63 to -0.16).

There is evidence suggesting that there is no clinically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms by the end of treatment as measured by the HRSD (N= 4; n= 336; Random effects WMD= 0.35; 95% CI, -1.84 to 2.55).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on increasing the likelihood of achieving remission by the end of treatment as measured by the BDI (N= 1; n= 116; RR= 1.43; 95% CI, 0.85 to 2.39).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N= 1; n= 116; RR= 1.43; 95% CI, 0.85 to 2.39).

Effect of treatment on efficacy outcomes at one-year follow-up

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on increasing the likelihood of achieving remission at one year follow-up as measured by the HRSD (N= 1; n= 116; RR= 0.93; 95% CI, 0.59 to 1.45).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms at one year follow-up as measured by the HRSD (N= 1; n= 55; WMD= -1.4; 95% CI, -5 to 2.2).

There is evidence suggesting that there is no clinically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms at one year follow-up as measured by the BDI (N= 3; n= 264; WMD= -0.99; 95% CI, -3.16 to 1.17).

6.10.3.2 Short-term psychotherapies versus placebo or wait list control

Tolerability and acceptability of treatment

There is strong evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on

reducing the likelihood of leaving treatment early for any reason (N= 1; n= 60; RR= 0.11; 95% CI, 0.03 to 0.44).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and placebo or wait list control on reducing the likelihood of leaving treatment early due to side effects (N= 1; n= 60; RR= 0.2; 95% CI, 0.01 to 4).

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on reducing depression symptoms by the end of treatment as measured by the BDI (N= 2; n= 79; WMD= -7.41; 95% CI, -11.96 to -2.85).

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on reducing depression symptoms by the end of treatment as measured by the HRSD (N= 1; n= 55; WMD= -4.7; 95% CI, -8.42 to -0.98).

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on increasing the likelihood of achieving remission by the end of treatment as measured by the BDI (N= 2; n= 84; RR= 0.65; 95% CI, 0.45 to 0.93).

There is strong evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N= 2; n= 84; RR= 0.52; 95% CI, 0.35 to 0.77).

6.10.4 Clinical summary

Short-term psychological therapies (problem-solving therapy or CBT) are more effective and more acceptable to patients than either placebo or wait list control. There is evidence that there is no difference in efficacy between short-term psychological therapies (CBT, problem-solving therapy and counselling) and other treatments (mostly antidepressants and GP care), although psychological therapy appears to be more tolerable.

6.11 Clinical practice recommendations for psychological interventions

6.11.1.1 When considering treatment for older adults, healthcare professionals should be aware that older adults with depression may respond as well

to psychological interventions as do younger people and therefore the full range of psychological interventions should be made available to them. (C)

6.11.1.2 In both mild and moderate depression psychological treatment specifically focused on depression (problem solving therapy, brief CBT and counselling) of 6 to 8 sessions over 10 to 12 weeks should be considered. (B)

6.11.1.3 When considering individual psychological treatments for moderate, severe and refractory depression, the treatment of choice is CBT. Where the patient expresses a preference for IPT or, in the view of the healthcare professional, the patient may benefit from IPT, then IPT should be considered. (B)

6.11.1.4 For moderate and severe depression the duration of all psychological treatments should typically be in the range of 16 to 20 sessions over 6 to 9 months. (B)

6.11.1.5 In moderate to severe depression antidepressant medication should be routinely offered to all patients before psychological interventions. (A)

6.11.1.6 For patients with moderate or severe depression who do not take or who refuse antidepressant treatment, CBT should be offered. (B)

6.11.1.7 Where patients have responded to a course of CBT consideration should be given to follow-up sessions, which typically consist of 2 to 4 sessions over 12 months. (B)

6.11.1.8 For patients with depression who have a regular partner and who have not benefited from a brief individual intervention, couples therapy should be considered. An adequate course of couples therapy should be 15 to 20 sessions over 5 to 6 months**. (C**)

6.11.1.9 For patients who have not had an adequate response to a range of other treatments for depression (for example, antidepressants and brief psychological interventions) consideration should be given to a course of CBT**. (C)**

6.11.1.10 For patients with recurrent depression, who have relapsed despite antidepressant treatment, or who express a preference for psychological interventions, CBT should be considered. (C)

6.11.1.11 For patients whose depression is refractory the combination of antidepressant medication with CBT should be considered. (B)

6.11.1.12 For patients with severe depression in whom avoidance of side effects often associated with antidepressants is a clinical priority or personal preference, CBT should be considered. (B)

6.11.1.13 For patients with severe depression who are starting a course of CBT, consideration should be given to providing 2 sessions per week for the first month of treatment. (C)

6.11.1.14 For patients with chronic depression a combination of CBT and antidepressant medication should be offered. (A)

6.11.1.15 For patients with severe depression who decline an offer of CBT, antidepressants or a combination of the two, consideration may be given to IPT, preferably in combination with antidepressants. (C)

6.11.1.16 For patients with recurrent moderate depression who have relapsed whilst following, or after finishing, a course of antidepressants, the combination of antidepressant medication with CBT should be considered. (B) [change]

6.11.1.17 Where a patient with depression has a previous history of relapse and poor or limited response to other interventions, consideration should be given to CBT. (B)

6.11.1.18 CBT should be considered as a prophylactic for patients who have experienced 2 previous episodes of moderate or severe depression. (C)

6.11.1.19 Mindfulness-based CBT, usually delivered in a group format, should be considered for people who are currently well but have

experienced 3 or more previous episodes of depression because this may significantly reduce the likelihood of future relapse. (B)

6.11.1.20 When patients with moderate or severe depression have responded to another intervention but are unable or unwilling to continue with that intervention, and are assessed as being at significant risk of relapse, consideration should be given to a maintenance course of CBT. (B)

6.11.1.21 There is insufficient evidence on which to recommend the routine use of psychodynamic psychotherapy. However, psychodynamic therapy may be of value in the treatment of the complex comorbidities that may be present along with depression. (C)

6.12 Research recommendations for psychological interventions

Adequately powered RCTs reporting all relevant outcomes, including relapse rates, comparing the efficacy of different models of CBT, IPT and BT should be undertaken in order to identify differential individual response to treatment, including severity of baseline depression symptoms.

An adequately powered RCT reporting all relevant outcomes to assess the efficacy of problem-solving therapy for moderate depression in primary care should be undertaken.

An adequately powered RCT reporting all relevant outcomes to assess the efficacy of short-term psychodynamic therapy for depression should be undertaken.

7 Introduction to pharmacological interventions in the treatment and management of depression

This chapter introduces the pharmacological interventions in the management of depression covered by this guideline. It discusses some of the issues that the GDG addressed in assessing the evidence base in order to form recommendations, including that of placebo response. The reviews of pharmacological interventions themselves are presented in the following chapter.

7.1 Introduction

Since the introduction of the first tricyclic (TCA) antidepressant imipramine in 1957 many new antidepressants have been introduced and currently approximately 35 different antidepressants in a number of classes are available worldwide. Over the succeeding 45 years there has been intensive research on the effects of drug therapy on depression and how drugs might alter the natural history of the disorder. A large number of reviews and meta-analyses are available. It is beyond the scope of this document to provide a comprehensive literature review of every drug or discuss the plethora of guidelines that have been produced over the last ten years. Excellent reviews of the topic are to be found in the British Association for Psychopharmacology Evidence Based Guidelines for Treatment of Depressive Disorder (Anderson et al 2000) and in the World Federation Society of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Unipolar Depressive Disorders Part I and II (Bauer et al 2002a, Bauer et al., 2002b).

Differences in outcome between antidepressant drug treated and untreated major depression are difficult to demonstrate in naturalistic studies (Ronalds et al., 1997). A possible reason is that treatment is often inadequate with less than 50% of patients with major depression receiving the recommended intensity of antidepressant drug treatment. There is some evidence: an untreated depressive episode typically lasts about six months or longer (Angst & Preisig, 1995) but in a ten-year prospective study of 258 subjects with treated unipolar depression the duration of recurrent mood disorders averaged approximately 20 weeks (Solomon et al 1997). Short-term response rates in intention-to-treat samples are approximately 50-65% on antidepressants compared with 25 to 30% on placebo in randomised controlled trials (Shulberg et al., 1999). In a naturalistic study without a placebo, recovery rates in moderately depressed patients randomised to treatment as usual were much lower at eight months (only 20%) than those randomised to psychotherapy or antidepressant drug treatment (approximately 50%) (Schulberg et al, 1996).

There is strongest evidence for efficacy of medication when treating major depression of at least moderate severity. In primary care a greater adequacy of treatment has not been shown to improve clinical outcome significantly (Simon et al 1995), whereas there is some evidence that outcome may improve in more severely ill patients in psychiatric care (Ramana et al., 1999). A likely reason is that up to half of patients in primary care have mild major depression as defined by DSM-IV where efficacy of antidepressant treatment is unproven (Schwenk et al 1996). Scores on the Hamilton Rating Scale for Depression (HRSD) in these patients are generally between 12 and 16. Paykel et al (1998) found that patients with HRSD scores of 13 or greater benefited from amitriptyline compared with placebo treatment, but in those with scores below 13 response was equally good on both treatments. Ottevanger (1991) found a higher threshold of HRSD scores (17 to 18) before antidepressants were of benefit over placebo.

Systematic reviews using meta-analysis suggest that the commonly available antidepressants have comparable efficacy in the majority of patients seen in primary care or outpatient settings (Anderson 1999, Geddes et al 1999). There is little consensus

on the relationship between clinical typology and outcome with antidepressants. Some evidence suggests that monoamine oxidase inhibitors (MAOIs) may be less effective than TCAs in hospitalised patients but more effective in non-hospitalised patients with atypical depression. It appears likely that this difference is due to the relative inefficacy of imipramine in atypical patients. The reviews cited above suggested that TCAs may be more effective than selective serotonin reuptake inhibitors (SSRIs) in patients hospitalised for major depression and that dual-action antidepressants (i.e., actions on both 5-HT and noradrenaline) without some of the side effects of the older tricylics may be more effective than SSRIs for major depression of at least moderate severity. There is some evidence that new antidepressants are better tolerated than older tricyclics and also that they are safer in overdose. SSRIs are more likely than older tricyclics to be prescribed at recommended doses for adequate periods (see *Current Practice of Antidepressant Prescribing in the UK* below). There are concerns over side effects following short- and long-term treatment which limit adherence to treatment with antidepressants. There is general agreement that adherence to treatment with medication is poor and evidence that this is improved by drug counselling but not by information leaflets alone. The side effects from antidepressant medication are dose-related and, in general (see below), there is evidence that an adequate dose of a tricyclic is 100 mg or above.

There is evidence that earlier non-persistent improvement in depressive symptoms may be due to a placebo response (Quitkin et al, 1987). An eventual response is unlikely if no improvement is evident after four weeks of treatment although older adults may take longer to respond (Anderson et al, 2000). At the present time there are a variety of strategies for improving efficacy following initial non-response which are supported by existing guidelines or systematic reviews using meta-analyses including lithium, the addition of thyroid hormones, adjunctive psychotherapy and dose escalation. Analysis of these modalities is a major feature of this current review.

In view of the high relapse or recurrence rate in depression it is currently recommended that antidepressant drug treatment is continued for a minimum of six months after remission of major depression (twelve months in older adults). It is recommended that the same dose of antidepressant is used in this continuation phase. It is also recommended that patients with recurrent major depression should go on to receive maintenance antidepressant drug treatment (Geddes et al., 2002). There is good evidence that patients with residual symptoms are at increasing risk of relapse of major depression and the current practice is to continue treatment for longer in those patients. The recurrence rate is lower when treatment is maintained with the effective acute treatment dose compared with the reduction to half the dose. There is some evidence lithium is an alternative for maintenance treatment and is recommended as an effective second-line alternative to antidepressants for maintenance treatment (Anderson et al, 2000).

There is good evidence that discontinuation symptoms may occur on abruptly stopping all classes of antidepressants. They are usually mild and self-limiting, but can occasionally be severe and prolonged. Some symptoms are more likely with individual drugs (Lejoyeux et al., 1996, Haddad, 2001). This effect appears more common with longer treatment. The syndrome generally resolves rapidly with reinstatement or within a few days to weeks without reinstatement. Discontinuation symptoms differ in pattern from those of a depressive relapse. It is generally recommended that patients should be warned that a discontinuation reaction may occur if treatment is abruptly stopped. It is recommended currently that all antidepressants are tapered in dose and frequency over a minimum of two weeks except in the situation where a patient switches into a hypomanic state. Some authorities recommend tapering the dose over six months in patients who have been on long-term maintenance treatment . If a discontinuation reaction does occur explanation and reassurance is often all that is required but if this is not sufficient and/or the reaction is more severe antidepressant treatment should be restarted and tapered more slowly.

7.2 Dose and duration of antidepressant treatment: evidence from clinical practice

7.2.1 Prevalence of Antidepressant Prescribing

In 1992 the Royal College of Psychiatrists launched the 'Defeat Depression' campaign to raise public awareness of depression and improve treatment (Viz & Priest, 1993). During the launch year, 9.9 million prescriptions for antidepressants were dispensed by community pharmacists in England, at a total cost of £18.1 million. However, an epidemiological study conducted in 1995 found that treatment remained suboptimal (Lepine et al, 1997). Only a third of people with major depression in the UK received a prescription usually, but not always, for an antidepressant drug. The number of prescriptions for antidepressant drugs dispensed in England has been increasing steadily since 1992 and reached 23.3 million in 2002. Spend on antidepressant drugs reached £380.9 million in 2002. Details of numbers of prescriptions and cost of individual drugs are on the Department of Health website (DOH website).

7.2.2 Dose

Studies of prescribing practice have generally taken 125 mg of TCAs (except lofepramine) and licensed doses of SSRIs to be "an effective dose" and compared prescribing in practice to this ideal. It is generally accepted that response to TCAs is partially dose-related but no such effect has been demonstrated for SSRIs. SSRIs are consistently found to be prescribed 'at an effective dose' in a much greater proportion of cases than TCAs. For example, a UK prescribing study that included data from over 750,000 patient records found that, if lofepramine was excluded, the mean doses prescribed for individual TCAs fell between 58 mg and 80 mg. Only 13.1% of TCA

prescriptions were for 'an effective dose' compared with 99.9% of prescriptions for SSRIs (Donoghue et al., 1996). A further UK study that followed prescribing for 20,195 GP patients found that at least 72% of those prescribed TCAs never received 'an effective dose' compared with 8% of those prescribed SSRIs (MacDonald et al., 1996). The prescribing of TCAs in this way is known to be pervasive across different countries and over time (Donoghue, 2000, Donoghue et al., 2001).

7.2.3 Duration

In a UK study of 16,204 patients who were prescribed TCAs or SSRIs by their GP, 33% of those prescribed an SSRI completed 'an adequate period of treatment' compared with 6% of those prescribed a TCA (2.8% if lofepramine was excluded) (Dunn et al, 1999). 'An adequate period of treatment' was defined by the authors as: prescriptions covering at least 120 days treatment within the first 6 months after diagnosis.

There is some evidence that the mean figure quoted for SSRIs may mask important differences between drugs: Donoghue (2000) found that, in a GP population of 6150 patients who were prescribed SSRIs, 27% of fluoxetine patients were still receiving prescriptions after 120 days compared with 23% of paroxetine patients and 13.5% of sertraline patients. Of course, prescribing patterns cannot be directly linked with outcome in studies of this type.

An RCT conduced in the USA randomised 536 adults to receive desipramine, imipramine or fluoxetine (Simon et al, 1996). Sixty percent of the fluoxetine patients completed 6 months of treatment compared with less than 40% of the TCA patients. Those who discontinued one antidepressant were offered another. There were no differences in overall completers or response rates at endpoint suggesting that initial drug choice did not affect outcome. However, patients outside of clinical trials may not return to their GP to have their treatment changed and outcome may be less positive. For example: A Swedish study of 949 patients found that 35% only ever received one prescription irrespective of whether it was for a TCA or a SSRI (Isacsson et al, 1999). After six months, 42% of SSRI patients were still receiving prescriptions compared with 27% of TCA patients. There is some evidence from this study that the relapse rate may have been higher in the TCA group: 28% of TCA treated patients received a subsequent prescription for an antidepressant after a nine-month treatment-free gap compared with 10% of SSRI patients.

7.3 Limitations of the literature: problems with randomised controlled trials (RCTs) in pharmacology

In RCTs, patients assigned to the 'placebo' arm receive regular visits to their doctor, supportive help, and a kindly interest in their welfare. In some trials the participants are allowed to contact the therapist at any time to report problems. In short, they receive everything except the pharmacological help from the tablet in the "active drug" arm of the trial. This constitutes a treatment in itself, and almost 30% of patients assigned to placebo respond within 6 weeks (Walsh et al 2002). This recovery has two components: the spontaneous recovery of the disorder itself; and the additional recovery due to supportive care.

Spontaneous recovery is a function of severity of the disorder; with lesser degrees of depression the recovery is greater. Unfortunately there is a tendency for investigators to recruit patients with less severe depression to the RCTs, and these are more likely to recover spontaneously (Khan et al 2002).

Conversely, the more severely depressed patients are less likely to be thought suitable for RCTs (despite being more likely to show a true drug effect (Angst 1992; Khan et al 2002)), since clinicians are reluctant to allow suicidal patients, or patients with severe degrees of depressive phenomena, to run the risk of an inactive treatment.

Next, of those offered to the RCT a full 40% fail to complete the study – either because they drop out of treatment themselves, or are withdrawn from the RCT by the anxious clinician (Stassen et al., 1994). Worse still, results are often presented only for 'completers', rather than being 'intention to treat' studies (This report).

Finally, some participants may not be representative of patients seen in clinical practice, as they are recruited by newspaper advertisement and paid for their participation in the study after completing a screening questionnaire (Greist et al 2002; Thase 2002).

The inclusion of individuals likely to improve, whatever they are given, as well as those motivated to receive free medication, taken together with the smaller likelihood of severely depressed patients being included, will all reduce the size of the specific drug effect. Confining the study to 'completers' introducers unknown biases into a cloudy picture.

Most studies of the effects of drugs are sponsored by the drug industry, and these have been shown to be more than 4 times as likely to demonstrate positive effects of the sponsor's drug as independent studies (Lexchin et al., 2003). Finally, the tendency of journal editors to publish only studies with positive results (Kirsch 2001; Melander et al 2003), and the fact that the same patients may appear in several publications (op.cit) introduces a severe bias in the other direction.

Despite the limitations of RCTs described above, the bulk of our recommendations are based on RCT evidence, However, we have been careful to consider their application to routine practice as evidenced by our use of both a number of [C] level recommendations and in our 'Good Practice Points'.

7.4 The placebo response

In addition to the points made above, in recent years there has been an increasing response to placebo, so that the extent of the placebo response correlates with the year of publication (r = +0.43) (Walsh et al., 2002). There is a similar, but less robust, association between extent of the response to active medication and year of publication (r = +0.26) (ibid.). This may well indicate an increasing tendency for RCTs to be carried out on people with mild disorders and disorders that would have remitted spontaneously.

A final important point is that there is evidence that the placebo response is greatest with mild depression, and the drug-placebo difference becomes greater with increasing degrees of severity of depression (Angst, 1992; Khan et al., 2002). This effect cannot be demonstrated in the meta-analyses carried out for the present report since the published studies do not quote data for individual patients, but only for the entire group. Thus, there is considerable overlap between the distributions of HRSD scores between inpatient and outpatient studies, so that the effect is diluted.

Further issues concerning placebo response are discussed below.

7.5 Studies considered for review – additional inclusion criteria

In addition to the criteria established for the inclusion of trials for the guideline as a whole, the following specific criteria relating to RCTs of pharmacological treatments were established by the Pharmacology Topic Group:

7.5.1 Diagnosis

- Trials where some participants had a primary diagnosis of bipolar disorder were included provided at least 85% had a primary diagnosis of major depressive disorder and no more than 15% had a primary diagnosis of bipolar disorder. These figures resulted from discussion, expert opinion and involvement with user groups as those likely to identify a study that had some validity for determining efficacy in major depressive disorder.
- Trials where some participants had a primary diagnosis of dysthymia were included provided at least 80% of trial participants had a primary diagnosis of major depressive disorder, and no more than 20% had a primary diagnosis of dysthymia
- Trials where participants had a diagnosis of atypical depression were included provided all had a primary diagnosis of major depressive disorder.

- Studies were included provided data from the HRSD and Montgomery Asberg Depression Rating Scale (MADRS) could be extracted for the following outcomes:
  - The number of participants who remitted[13] (achieved below the equivalent 17-item HRSD score of 8)
  - The number of participant who responded[14] (achieved at least a 50% reduction in scores)
  - Mean endpoint or change scores

[13] For statistical reasons, relative risks for this outcome are framed in terms of the number of participants not remitting.
[14] For statistical reasons, relative risks for this outcome are framed in terms of the number of participants not responding.

7.5.2 Dose

There is prima facie evidence that doses of tricyclics below 100 mg are less effective than doses above (Blashky et al, 1971, Thompson et al, 1989, Bollini et al,1999). Studies were included provided there? was clear evidence that at least 75% of patients received the standard dose or the mean dose used was at least 105% of the standard dose. The standard dose was either that stated by Bollini et al (1999) or for drugs not included by Bollini et al, the dose stated by the BNF (March 2003).

7.6 Issues and topics covered by this review

In view of the vast numbers of studies performed investigating pharmacological responses in depression and the limited time available, the Pharmacology Topic Group had to decide which aspects of drug treatment were most important to clinicians and patients. This chapter therefore is not the result of a comprehensive review of all psychopharmacological studies performed in all aspects of the treatment of depression

7.6.1 Severity

A key issue is whether severity of illness can guide the use of antidepressant medication. Unfortunately there is little data to help with this point. Although most studies report mean baseline HRSD or MADRS, this can be taken only as a guide to baseline severity because of hetereogenous samples with wide standard deviations as well as the fact that results are not presented in a way that allows differential response to be identified.

7.6.2 Setting

Where appropriate studies were categorised by setting: (a) primary care (where this was specifically stated), (b) inpatients - where at least 75% of the patients were initially treated as inpatients, (c) outpatients/secondary care – studies in which this was specified. This is likely to provide some bearing on the issue of setting and type of depression although it is not clear how well setting maps onto severity. A further problem is that because of differences between health-care systems across the world, the nature of the patients in these different groups varies. Thus considerable uncertainty must be associated with conclusions drawn using these categories.

7.6.3 Issues addressed

In broad terms we have tried to address the issue of the comparative efficacy, acceptability and tolerability of the antidepressants most commonly prescribed in the UK, together with specific pharmacological strategies for dealing with refractory, atypical and psychotic depression. Within each review, where the data allowed, we have looked at the effect on outcomes of severity, setting and age. In addition, we have looked at some of the issues regarding so called continuation and maintenance therapy, the cardiac safety of antidepressants, dosage, and issues regarding suicidality and completed suicide with antidepressants. Although the number of trial participants leaving treatment early was used as a measure of the tolerability of drugs reviewed, this guideline cannot be seen as a comprehensive review of the issue of the safety, pharmacology, pharmokinetics and pharmaceutical advice regarding these drugs. Readers are referred to conventional texts particularly regarding issues of dosage

schedules, acceptability and tolerability for individual patients and regarding drug interactions.

7.6.4 Topics covered

The following topics are covered:

This chapter	Review of SSRIs versus placebo
Chapter 8 (Section 8.1)	Use of individual drugs in the treatment of depression - TCAs (amitriptyline and overview of TCA data) - Selective serotonin reuptake inhibitors (SSRIs): citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline - Monoamine-oxidase inhibitors (MAOIs): phenelzine - 'Third-generation' drugs: mirtazapine, reboxetine and venlafaxine - St John's wort
Chapter 8 (Section 8.2)	Factors effecting antidepressant choice - The pharmacological management of depression in older adults - The effect of gender on the pharmacological management of depression - The pharmacological management of psychotic depression - The pharmacological management of psychotic depression - The pharmacological management of atypical depression - The pharmacological management of relapse prevention - Dosage issues - Antidepressant discontinuation symptoms - The cardio-toxicity of antidepressants - Suicidality
Chapter 8 (Section 8.3)	The treatment of refractory depression - Switching strategies - Venlafaxine for treatment resistant depression - Augmentation strategies ▪ Augmenting an antidepressant with lithium ▪ Augmenting an antidepressant with anticonvulsants (lamotrigine, carbamazepine or valproate) ▪ Augmenting an antidepressant with another antidepressant

- Augmenting an antidepressant with pindolol
- Augmenting an antidepressant with T3
- Augmenting an antidepressant with a benzodiazepine
- Augmenting an antidepressant with an antipsychotic
- Augmenting an antidepressant with buspirone

7.7 Review of SSRIs versus placebo

7.7.1 Introduction

A placebo is an inert or innocuous substance used in controlled trials to test the efficacy of an active drug. Placebos began to be used increasingly in control conditions in clinical trials during the 1950s, although at that time they often contained an active ingredient. The response of patients to the inert substances now used should not be equated with the untreated course of the disorder, as there is a pronounced therapeutic advantage in being seen regularly and being offered clinical care, irrespective of the contents of the tablet or the nature of the psychological intervention.

In two meta-analyses (Kirsch & Sapirstein (1998); Kirsch et al (2002)) it was argued that up to 80% of the effect of antidepressants may be duplicated by placebo – i.e. that 80% of the effect of antidepressants is placebo response. Although the earlier meta-analysis was criticised because it included only a limited number of published trials, the later work analysed all data submitted to the US Food and Drug Administration (FDA) for the licensing of new antidepressants, including the SSRIs and venlafaxine, although it is not clear how many of the trials involved have subsequently been published.

Many commentators attribute this finding to expectancy effects. There is also the problem of 'breaking the blind' as a result of antidepressant side effects (Rabkin et al., 1986, in Kirsch & Scoboria, 2002) leading to possible bias in placebo-controlled clinical trials. One way round this problem is to use an active placebo. A meta-analysis of trials using this technique indicated that the placebo effect of antidepressants may be even stronger than that indicated by analyses of trials using inactive placebos. However, there are few trials of active placebo using modern diagnostic criteria and widely accepted ratings (Moncrieff et al, 2001). Psychological factors arising from trial methodology influencing the placebo response include the encouraging effect of being in treatment (Andrews, 2001), demand characteristics (Salamone, 2000) and even the trial recruitment and assessment process itself (ibid.).

It has been suggested that response rates to both placebo and active drugs are increasing at a rate of 7% a year (Walsh et al, 2002). This may be due in part to increased trial recruitment via media advertising, the fact that participants in RCTs are often paid, and the reluctance of trialists to offer placebos to severely ill patients. The resulting participants in RCTs tend to have milder, less chronic depression which is more responsive to placebo compared to that in participants from clinical referral (ibid.). Once

placebo response rates are above 40%, an active drug effect becomes harder to detect, particularly since many trials are underpowered (Thase, 2002). Other methodological problems are highlighted by inter-site differences found in many multi-site trials probably resulting from subtly different procedures being adopted by different researchers (Schneider & Small, 2002).

Non-methodology-related explanations for the placebo response include the effect of spontaneous remission (which may be as high as 50% within an eight-week period, the length of many trials (Andrews, 2001)).

The placebo response may also be short-lived, with more patients on placebo relapsing compared to those on antidepressants (Ross et al, 2002). Longer trials are required to be able to fully elucidate the contributions of placebo and the treatment to clinical response. Dago & Quitkin (1995) suggest that greater placebo response is more likely when the presenting episode occurs within the context of a psychosocial stressor.

There is convergent evidence that the placebo response is less marked as clinical severity increases, and the size of the drug/placebo difference becomes greater (Elkin et al 1989; Angst 1993; Khan et al 2002). Thus, the additional therapeutic effects of antidepressants may be submerged by the size of non-specific effects when mainly mildly depressed patients are studied. The published data did not allow the GDG to address this problem systematically since most RCTs merely give mean depression scores (with standard deviations) of large groups of patients, so that there is very considerable overlap between baseline depression scores of patients in different studies. It was therefore only possible to address important questions relating to the effects of severity, age and gender with relatively weak information about patient characteristics. Nonetheless, our findings are in favour of greater drug/PBO differences with increasing severity (see below). It should also be borne in mind that there are non mood-related benefits of prescribing antidepressants, for example, in helping patients to sleep better and in dealing with anxiety-related symptoms. Improving these factors may help patients to cope with their daily lives thereby contributing to a reduction in depression symptoms.

7.7.2 Studies considered for review [15][16]

One hundred and three studies were found in a search of electronic databases with 48[17] being included and 55 being excluded by the GDG.

---

[15] Full details of the search strategy for this and other reviews in the guideline are available on request from the NCCMH. Details of standard search strings used in all searches are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17, which also contains a list of excluded studies with reasons for exclusions.

[16] Here and elsewhere in the guideline, each study considered for review is referred to by a 'study ID' made up of first author and publication date (unless a study is in press or only submitted for publication, when first author only is used).

[17] This figure includes a multicentre trial (KASPER1995) as well as two of its constituent trials published independently (DOMINQUEZ1985, LAPIERRE1987) because 'number of participants leaving the study early for any reason' was not extractable from KASPER1995.

Six studies were of citalopram (BURKE01, FEIGHNER99, MENDLES1999, MONT'MERY01, MONT'MERY92A, STAHL00); seventeen of fluoxetine (ANDREOLI2002, BYERLEY88, COHN1985, COLEMAN01, DUNLOP1990, FEIGHNER89A, MCGRATH00, O'FLYNN1991, RICKELS1986, RUDOLPH99, SIL'STNE99, SRAMEK95, STARK85, THAKORE1995, VALDUCCI1992, WERNICKE1987, WERNICKE1988); twelve of fluvoxamine (CLAGHORN1996, CONTI1988, DOMINQUEZ85, FABRE1996, FEIGNER1989, ITIL1983, KASPER95, LYDIARD1989, LAPIERRE1987, NORTON1984, ROTH90, WALCZAK1996); eight of paroxetine (CLAGHORN92A, EDWARDS93, FEIGHNER92, HACKETT1996, MILLER1989, RICKELS1989, RICKELS1992, SMITH1992) and five of sertraline (COLEMAN1999, CROFT1999, FABRE95, RAVINDRAM1995, REIMHERR90). These provided data from up to 7,460 trial participants.

All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.75 weeks), with sixteen trials of eight weeks or longer. Three studies were of inpatients, 31 of outpatients, one in primary care and thirteen either mixed or unspecified. In no study were more than 80% of study participants aged 65 years and over. It was possible to determine baseline severity in 19 studies, with four being classified as moderate, six as severe and nine as very severe.

Visual inspection of funnel plots of the meta-analyses of the above studies indicated the possibility of publication bias. It was planned to combine these data with the FDA data reported by Kirsch et al (2002). However, it was not possible to determine which of the FDA data had been subsequently published.

Since it is possible that a placebo response is only short-lived, a sub-analysis of studies which lasted eight weeks or longer was undertaken.

7.7.3 Evidence statements[18]

Effect of treatment on response

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo with on achieving a 50% reduction in depression symptoms (N = 17[19]; n = 3143; RR = 0.73; 95% CI, 0.69 to 0.78).

In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms (N= 3[20]; n= 729; RR= 0.75; 95% CI, 0.65 to 0.87).

---

[18] The full list of all evidence statements generated from meta-analyses (and the associated forest plots) will be available on the CD-ROM that accompanies the guideline.

[19] Fifteen studies were excluded from all efficacy outcomes because >50% left treatment early (DOMINGUEZ85, CLAGHORN1996, COHN1985, CONTI1988, EDWARDS93, FABRE95, FABRE1996, FEIGHNER1989, FEIGHNER92, ITIL1983, LAPIERRE1987, SMITH1992, STAHL00, STARK85, WALZAK1996,)

[20] Studies were excluded from sub-analyses of severity if mean baseline scores were not available.

In severe depression there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms (N= 5; n= 619; RR= 0.63; 95% CI, 0.54 to 0.73).

In very severe depression there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms (N= 6; n= 866; RR= 0.72; 95% CI, 0.65 to 0.8).

Effect of treatment on remission rates

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs over placebo on increasing the likelihood of achieving remission (N= 3; n= 468; Random effects: RR= 0.8; 95% CI, 0.61 to 1.06).

Effect of treatment on mean end-point or change scores

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms but the size of this difference is unlikely to be of clinical significance (N= 16; n= 2223; SMD= -0.32; 95% CI, -0.41 to -0.24).

In moderate depression there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms but the size of this difference is unlikely to be of clinical significance (N= 2; n= 386; SMD= -0.28; 95% CI, -0.48 to -0.08).

In severe depression there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on reducing depression symptoms (N= 4; n= 344; SMD= -0.61; 95% CI, -0.83 to -0.4).

In very severe depression there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms but the size of this difference is unlikely to be of clinical significance (N= 5; n= 726; SMD= -0.39; 95% CI, -0.54 to -0.24).

Acceptability of treatment

There is evidence suggesting that there is a statistically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early but the size of this difference is unlikely to be of clinical significance (N= 39[21]; n= 7274; RR= 0.94; 95% CI, 0.88 to 0.99).

There is strong evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early due to side effects (N= 39; n= 7460; RR= 2.45; 95% CI, 2.08 to 2.89).

[21] One study (COHN1985) was removed from the meta-analysis to remove heterogeneity from the dataset.

There is some evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of experiencing side effects (N= 11; n= 2290; RR= 1.19; 95% CI, 1.13 to 1.25).

Sub-analysis of trials lasting eight weeks or longer

In order to assess whether the placebo effect was short-lived, trials lasting eight weeks or longer were analysed separately.

Effect of treatment on response in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms (N=8; n=1764; RR=0.72; 95% CI, 0.66 to 0.79).

In moderate depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms (N= 3; n= 729; RR= 0.75; 95% CI, 0.65 to 0.87).

In severe depression in trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms (N= 3; n= 535; RR= 0.63; 95% CI, 0.53 to 0.74).

In very severe depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on achieving a 50% reduction in depression symptoms N= 1; n= 299; RR= 0.72; 95% CI, 0.59 to 0.88).

Effect of treatment on remission in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and placebo on increasing the likelihood of achieving remission.

Effect of treatment on mean endpoint scores in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms but the size of this difference is unlikely to be of clinical significance (N= 7; n= 1369; SMD= -0.29; 95% CI, -0.39 to -0.18).

In moderate depression in trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms but the size of this difference is unlikely to be of clinical significance (N= 2; n= 386; SMD= -0.28; 95% CI, -0.48 to -0.08).

In severe depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on reducing depression symptoms (N= 1; n= 237; SMD= -0.53; 95% CI, -0.79 to -0.27).

In very severe depression in trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms but the size of this difference is unlikely to be of clinical significance (N= 1; n= 283; SMD= -0.43; 95% CI, -0.67 to -0.2).

Acceptability of treatment in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is evidence suggesting that there is no clinically significant difference between SSRIs and placebo on reducing the likelihood of leaving treatment early (N= 13; n= 3069; RR= 0.96; 95% CI, 0.88 to 1.05).

In trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early due to side effects (N= 13; n= 3069; RR= 2.06; 95% CI, 1.59 to 2.68).

In trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring placebo over SSRIs on reducing the likelihood of experiencing side effects but the size of this difference is unlikely to be of clinical significance (N= 7; n= 1378; RR= 1.09; 95% CI, 1.03 to 1.16).

7.7.4 Clinical summary

There is strong evidence that antidepressants have greater efficacy than placebo on achieving a 50% reduction in depression scores in severe and very severe depression. There is some evidence for a similar effect in moderate depression. The effect was similar in longer trials. These results should be treated with caution because of publication bias (i.e., that studies with statistically significant findings are more likely to be published than those with non-significant findings).

There is insufficient evidence on the effect on remission because of heterogeneity in the meta-analysis, but the trend is towards a small effect size. There appears to be no difference between SSRIs and placebo on mean endpoint or change scores.

SSRIs produced more side effects than placebo, with more people leaving treatment early because of adverse events. This was also the case in trials lasting eight weeks or longer.

8 Pharmacological interventions in the treatment and management of depression

This chapter is in three sections:

- Use of individual drugs in the treatment of depression
- Factors that influence choice of antidepressant
- The pharmacological treatment of refractory depression

8.1 Use of individual drugs in the treatment of depression

8.1.1 Introduction

This section reviews the relative efficacy of individual antidepressants in the treatment of depression. Where there were sufficient data, the effect of patient setting (inpatient, outpatient or primary care) on choice of drug was also examined.

It covers the following drugs:

- Tricyclic antidepressants (TCAs)
    - Amitriptyline
    - An overview of TCAs*
- Selective serotonin reuptake inhibitors (SSRIs)
    - Citalopram
    - Fluoxetine
    - Fluvoxamine
    - Paroxetine
    - Sertraline
- Monoamine-oxidase inhibitors (MAOIs)
    - Phenelzine
- 'Third-generation' drugs
    - Mirtazapine

  - Reboxetine
  - Venlafaxine
- Herbal preparations:
  - St John's wort

* Many studies in the above reviews used a TCA as a comparator treatment. These data were combined in a review of TCAs to enable the GDG to gain an overview of this class of drugs.

8.1.2 Tricyclic antidepressants (TCAs)

8.1.2.1 Introduction

TCAs have been used to treat depression for over 40 years. Currently nine TCAs are available in the UK. They are thought to exert their therapeutic effect by inhibiting the re-uptake of monoamine neurotransmitters into the presynaptic neurone thus enhancing noradrenergic and serotonergic neurotransmission. Although all TCAs block the reuptake of both amines, they vary in their selectivity with, for example, clomipramine being primarily serotonergic and imipramine noradrenergic.

All TCAs cause, to varying degrees, anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention, sweating), sedation and postural hypotension. These side effects necessitate starting with a low dose and increasing slowly. In many patients a 'therapeutic dose' is never reached either because the patient cannot tolerate it or because the prescriber does not titrate the dose upwards.

All TCAs, except lofepramine, are toxic in overdose with seizures and arrhythmias being a particular concern (see sections 8.2.10 and 8.2.9). This toxicity, and the perceived poor tolerability of these drugs in general, has led to a decline in their use in the UK over the last decade.

8.1.2.2 Amitriptyline

Although amitriptyline was not the first TCA and is not the best tolerated or the most widely prescribed, it is the standard drug against which new antidepressants are compared with respect to both efficacy and tolerability. Amitriptyline may be marginally more effective than other antidepressants, a potential benefit that is offset by its poorer tolerability (Barbui & Hotopf, 2001). Efficacy benefits may be more marked in hospitalised patients (Anderson et al, 2000).

Studies considered for review[22] [23]

The GDG used an existing review (Barbui et al., 2001) as the basis for this section, for which the authors made their data available to the NCCMH team. The original review included 184 studies of which 144 did not meet the inclusion criteria set by the GDG. Eight additional studies were identified from searches undertaken for other sections of this guideline. Thus 48 trials are included in this section providing tolerability data from up to 4,484[24] participants and efficacy data from up to 2,760 participants. A total of 177 trials were excluded. The most common reason for exclusion was an inadequate diagnosis of depression.

All included studies were published between 1977 and 1999 and were between three and ten weeks long (mean = 5.71 weeks). Sixteen studies were of inpatients, 22 of outpatients and two were undertaken in primary care. In the remaining eight, it was either not clear from where participants were sourced or they were from mixed sources. In three all participants were over the age of 65 years (COHN1990, GERETSEGGER1995, HUTCHINSON1992). Studies reported mean doses of equivalent to at least 100 mg of amitriptyline.

Data were available to compare amitriptyline with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amoxapine, desipramine[25], dosulepin, doxepin, imipramine, lofepramine, minaprine[25], nortriptyline, trimipramine, maprotiline, mianserin, trazodone, phenelzine and mirtazapine.

The original systematic review on which this section is based included two outcome measures, responders and mean endpoint scores. It did not include data on remission and this has not been extracted for the present review.

---

[22] Full details of the search strategy for this and other reviews in the guideline are available on request from the NCCMH. Details of standard search strings used in all searches are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17, which also contains a list of excluded studies with reasons for exclusions.

[23] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

[24] It is not always possible to extract data for all outcomes from each study, therefore the figures given are for the outcome with the largest number of participants

[25] Not available in the UK

Evidence statements [26][27]

Effect of treatment on efficacy[28]

There appears to be no clinically important difference in efficacy between amitriptyline and other antidepressants, either when compared together or by class:

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on achieving a 50% reduction in depression scores as measured by the HRSD (N= 16; n= 1541; RR=1.06; 95% CI, 0.96 to 1.18).

There is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N= 32; n= 2760; SMD= 0.09; 95% CI, 0.01 to 0.16).

There is evidence suggesting that there is no clinically significant difference between:

- TCAs and amitriptyline on the likelihood of reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 5; n= 285; SMD= 0.04; 95% CI, -0.19 to 0.27)
- SSRIs and amitriptyline on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 9; n= 837; RR= 1.09; 95% CI, 0.95 to 1.25)
- SSRIs and amitriptyline on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 19; n= 1648; SMD= 0.06; 95% CI, -0.03 to 0.16).

There is insufficient evidence to determine whether there is a clinically significant difference between TCAs and amitriptyline on achieving a 50% reduction in depression symptoms.

---

[26] The full list of all evidence statements generated from meta-analyses (and the associated forest plots) will be available on the CD-ROM that accompanies the guideline.

[27] The authors of the review on which this review is based entered data into Review Manager so that amitriptyline is on the right-hand side of the forest plot and comparator treatments on the left.

[28] Where it made a difference to results the following studies were removed from efficacy analyses because >50% left treatment early: COHN1990, FAWCETT1989, GUY1983, WILCOX1994, PRESKORN1991, SHAW1986, STUPPAECK1994.

Effect of setting on treatment efficacy

There appears to be no clinically important difference between amitriptyline and other antidepressants in different treatment settings:

In inpatients there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 6; n= 600; RR= 1.08; 95% CI, 0.9 to 1.29).

In inpatients there is evidence suggesting that there is a statistically significant difference between other antidepressants and amitriptyline on the likelihood of reducing depression symptoms as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N= 11; n= 752; SMD= 0.16; 95% CI, 0.02 to 0.30).

In outpatients there is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms, but the size of this difference is unlikely to be of clinical significance (N= 9; n= 1,002; SMD= 0.13; 95% CI, 0.00 to 0.25).

In outpatients there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 7; n= 666; RR= 1.03; 95% CI, 0.89 to 1.2)

In patients in primary care there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline in the likelihood of reducing depression symptoms by the end of treatment as measured by the HRSD (N= 2; n= 132; SMD= -0.09; 95% CI, -0.44 to 0.27).

Acceptability and tolerability of treatment

When compared to all antidepressants, amitriptyline appears to be equally tolerable in terms of leaving treatment early for any reason. However, patients taking other antidepressants report fewer side effects:

There is evidence suggesting that there is no clinically significant difference between amitriptyline and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N= 43; n= 4884; RR= 0.92; 95% CI, 0.84 to 1.03).

There is strong evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of leaving the study early due to side effects (N= 34; n= 4034; RR= 0.71; 95% CI, 0.61 to 0.83).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline in patients with side effects (N= 5; n= 773; RR= 0.78; 95% CI, 0.65 to 0.93).

Acceptability and tolerability of treatment by setting

- For inpatients, there appears to be little difference between the tolerability of amitriptyline and other antidepressants:

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of inpatients leaving the study early for any reason (N= 15; n= 1320; RR= 0.96; 95% CI, 0.82 to 1.13).

There is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of inpatients leaving treatment early due to side effects (N= 8; n= 855; RR= 0.78; 95% CI, 0.55 to 1.1).

There is evidence suggesting that there is no clinically significant difference between paroxetine and amitriptyline in inpatients reporting side effects (N= 2; n= 131; RR= 0.88; 95% CI, 0.68 to 1.12).

-
- Amitriptyline was less well tolerated in outpatients:

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of outpatients leaving treatment early for any reason (N= 19; n= 2647; Random effects: RR=0.87; 95%CI, 0.72 to 1.06).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of outpatients leaving treatment early for any reason due to side effects (N= 18; n= 2396; RR= 0.75; 95% CI, 0.62 to 0.9).

There is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline in reducing the likelihood of outpatients reporting side effects (N= 2; n= 552; RR= 0.8; 95% CI, 0.61 to 1.04).

Although much of the evidence was too weak to make a valid comparison of tolerability in primary care, more patients reported side effects in amitriptyline than paroxetine, which was the only comparator drug available:

In patients in primary care there is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of leaving treatment early either for any reason or due to side effects.

There is some evidence suggesting that there is a clinically significant difference favouring paroxetine over amitriptyline in primary care patients reporting side effects (N= 1; n= 90; RR= 0.55; 95% CI, 0.35 to 0.86).

Clinical summary

- Amitriptyline is as effective as other antidepressants, although patients taking the drug report more adverse events and tend to leave treatment early due to side effects.

8.1.3 Tricyclic antidepressants – an overview of selected data

This section combines data from other reviews where a TCA was used as a comparator treatment. It is therefore not a systematic review since a systematic search for all trials of TCAs was not conducted. It specifically does not include comparisons of TCAs with other TCAs.

8.1.3.1 Studies considered for review

In all 94 studies from other reviews included a TCA as a comparator drug. Seventy studies were sourced from the review of SSRIs (section 8.1.6), seven from the review of mirtazapine (section 8.1.8.1), eight from phenelzine (section 8.1.7.1), three from reboxetine (section 8.1.8.2) and six from venlafaxine (section 8.1.8.3). Data were available from the following TCAs: clomipramine, doxepin, desipramine, imipramine, dosulepin, nortriptyline, amineptine and lofepramine. Efficacy data were available from up to 6,848 patients, and tolerability data from up to 8,967 patients.

All included studies were published between 1981 and 2002. Twenty-four studies were of inpatients, 48 of outpatients and three undertaken in primary care. In the remaining nineteen, it was either not clear from where participants were sourced or they were from mixed sources. In eleven more than 80% of study participants were aged 65 years and over, and in two participants had additional atypical features (QUITKIN1990, MCGRATH2000).

8.1.3.2 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there are statistically significant differences favouring alternative antidepressants over TCAs on the following outcomes, although the sizes of these differences are unlikely to be of clinical significance:

- achieving a 50% reduction in symptoms, (N= 17; n= 2756; RR= 0.9; 95% CI, 0.82 to 0.98)
- increasing the likelihood of achieving remission (N= 4; n= 819; RR= 0.86; 95% CI, 0.76 to 0.98).

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 70; n= 6,848; SMD= 0.02; 95% CI, -0.03 to 0.07).

Effect of setting on treatment efficacy

Inpatients

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on achieving a 50% reduction in depression symptoms in inpatients as measured by the HRSD (N= 5; n= 872; RR= 1.06; 95% CI, 0.9 to 1.24).

There is evidence suggesting that there is a statistically significant difference favouring TCAs over alternative antidepressants on reducing depression symptoms in inpatients by the end of treatment, but the size of this difference is unlikely to be of clinical significance. (N= 20; n= 1681; SMD= 0.12; 95% CI, 0.03 to 0.22).

Outpatients

There is some evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 5; n= 733; RR= 0.74; 95% CI, 0.64 to 0.87).

There is some evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on increasing the likelihood of achieving remission in outpatients by the end of treatment (N= 2; n= 345; RR= 0.75; 95% CI, 0.61 to 0.92).

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or MADRS (N= 33; n= 3275; SMD= -0.03; 95% CI, -0.1 to 0.04).

Primary care
There is insufficient evidence to determine whether there is a clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms in patients in primary care by the end of treatment as measured by the HRSD or MADRS (N= 2; n= 213; SMD= -0.14; 95% CI, -0.42 to 0.13).

Acceptability and tolerability of treatment
There is evidence suggesting that there are statistically significant differences favouring alternative antidepressants over TCAs on the following outcomes, but the size of these differences is unlikely to be of clinical significance:

- on reducing the likelihood of leaving treatment early for any reason (N= 83; n= 8967; RR= 0.88; 95% CI, 0.83 to 0.94)
- on reducing the likelihood of patients reporting adverse effects (N= 25; n= 3007; RR= 0.89; 95% CI, 0.86 to 0.93).

There is strong evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on reducing the likelihood of leaving treatment early due to side effects (N= 80; n= 8888; RR= 0.71; 95% CI, 0.65 to 0.78).

When TCAs were examined individually, only dosulepin appears to be more acceptable than alternative antidepressants:

There is some evidence suggesting that there is a clinically significant difference favouring dosulepin over alternative antidepressants on reducing the likelihood of leaving treatment early for any reason (N= 5; n= 336; RR= 1.42; 95% CI, 1.02 to 1.98).

8.1.3.3 Clinical summary
TCAs have equal efficacy compared with alternative antidepressants but are less well tolerated particularly in outpatients.

8.1.4 Selective serotonin reuptake inhibitors (SSRIs)
The selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin into the presynaptic neurone thus increasing neurotransmission. Although they 'selectively' inhibit serotonin reuptake, they are not serotonin

specific. Some of the drugs in this class also inhibit the reuptake of noradrenaline and/or dopamine to a lesser extent.

As a class, they are associated with less anticholinergic side effects and are less likely to cause postural hypotension or sedation. Dosage titration is not routinely required so subtherapeutic doses are less likely to be prescribed. They are also less cardiotoxic and much safer in overdose than the TCAs or MAOIs. These advantages have led to their widespread use as better tolerated first line antidepressants.

The most problematic side effects of this class of drugs are nausea, diarrhoea and headache. Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of various hepatic cytochrome metabolising enzymes (Mitchell, 1997) precipitating many significant drug interactions. Sertraline is less problematic although enzyme inhibition is dose related and citalopram is relatively safe in this regard.

There are other important differences between the SSRIs (Anderson & Edwards, 2001). These are outlined below:

Citalopram

Citalopram is the most serotonin selective of the SSRIs included in this section. In animals, one of its minor metabolites is cardiotoxic (Van der Burgh, 1994) and it is pro-convulsant at high dose (Boeck et al., 1982). The issue of its safety in overdose is discussed below (see Section 8.2.9.3). It is available as a generic preparation.

Fluoxetine

Fluoxetine is the most widely prescribed SSRI. It is associated with a lower incidence of nausea than fluvoxamine but a higher incidence of rash. It has a long half life which may cause problems with washout periods when switching to other antidepressant drugs but has the advantage of causing less discontinuation symptoms. It is available as a generic preparation.

Fluvoxamine

Fluvoxamine was the first of the currently available SSRIs to be marketed in the UK. It is associated with a higher incidence of nausea than the other SSRIs and so is not widely prescribed.

Paroxetine

Paroxetine is associated with a higher incidence of sweating, sedation and sexual dysfunction than other SSRIs and more problems on withdrawal (Anderson & Edwards, 2001, see also section 8.2.8 on antidepressant discontinuation symptoms). It is available as a generic preparation.

Sertraline

Sertraline is a well tolerated SSRI. It is more likely to be associated with upwards dosage titration during treatment than the other SSRIs (Gregor, 1994).

8.1.4.1 Studies considered for review

The GDG used an existing review (Geddes et al., 1999) as the basis for this review, for which the authors made their data available to the NCCMH team. The original review included 126 studies of which 51 did not meet the inclusion criteria set by the GDG. In addition one trial (Peselow et al., 1989) included in the original review was considered to be part of a multicentre trial (FEIGHNER92) rather than a separate trial. Another (FEIGHNER1989), excluded in the original review, was included in this review because it contained tolerability data (which the original review did not include). A further two trials excluded by the original review were also considered part of the FEIGHNER92 multicentre trial (Dunbar et al., 1991, Feigner et al., 1989c).

Since the original review compared SSRIs with TCAs only, 59 additional studies were identified from other reviews undertaken for this guideline, including two identified from hand searching reference lists. Thirty-three of these were included and 26 excluded. Thus 107 trials are included in this review providing data from up to 11,442 participants. A total of ninety-seven trials were excluded.

All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.5 weeks). Twenty-four studies were of inpatients, 51 of outpatients and six undertaken in primary care. In the remaining 26, it was either not clear from where participants were sourced or they were from mixed sources. In eleven more than 80% of study participants were aged 65 years and over (although only eight of these reported extractable efficacy outcomes). In one study participants had additional atypical features.

In addition to the standard diagnostic criteria, most studies required a minimum baseline HRSD score of between 10 and 22 on the 17-item version (61 studies) or between 18 and 22 on the 21-item version (28 studies). The ten studies reporting MADRS scores required minimum baseline scores of between 18 and 30.

Data were available to compare SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) with amineptine, amitriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, maprotiline, mianserin, trazodone, phenelzine, moclobemide, mirtazapine, venlafaxine and reboxetine.

The original systematic review on which this review is based and for which the data were made available to the GDG included only one outcome measure, mean endpoint scores, and did not include tolerability data. Tolerability data, but not additional efficacy outcomes, have been extracted by the NCCMH team.

Evidence statements

Effect of treatment on efficacy

There is no clinically significant difference between SSRIs and other antidepressants, whether combined as a group or divided by drug class:

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over SSRIs on overall efficacy, but the size of this difference is unlikely to be of clinical significance (N= 82[29]; n= 8,668; SMD= 0.08; 95% CI, 0.03 to 0.12).

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms as measured by the HRSD or MADRS between:

- SSRIs and TCAs (N= 49; n= 4,073; SMD= 0.05; 95% CI, -0.01 to 0.12)
- SSRIs and TCA-related antidepressants (N= 9; n= 461; SMD= -0.09; 95% CI, -0.28 to 0.09)
- SSRIs and MAOIs (N= 7; n= 469; SMD= 0.03; 95% CI, -0.15 to 0.22).

There is evidence suggesting that there is a statistically significant difference favouring third-generation[30] antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N= 17; n= 3665; SMD= 0.13; 95% CI, 0.06 to 0.19).

Effect of setting on treatment efficacy

In inpatients there is no difference between the efficacy of SSRIs and other antidepressants, apart from third-generation antidepressants:

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms in inpatients as measured by the HRSD or MADRS between:

- SSRIs and other antidepressants (N= 20; n= 1258; SMD= 0.09; 95% CI, -0.02 to 0.2)

[29] Studies where >50% of participants left treatment early were retained in the analysis since removing them made no difference to the results.

[30] Mirtazapine, venlafaxine and reboxetine.

- SSRIs and TCAs (N= 15; n= 970; SMD= 0.12; 95% CI, -0.01 to 0.24).

There is some evidence suggesting that there is a clinically significant difference favouring third-generation antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in inpatients (N= 1; n= 67; SMD= 0.58; 95% CI, 0.09 to 1.07).

There is insufficient evidence to determine whether there is a clinically significant difference either between SSRIs and MAOIs or between SSRIs and TCA-related antidepressants on reducing depression symptoms as measured by the HRSD or MADRS in inpatients.

In outpatients there is no difference between the efficacy of SSRIs and other antidepressants:

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients but the size of this difference is unlikely to be of clinical significance (N= 38; n= 4666; SMD= 0.06; 95% CI, 0 to 0.12).

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms as measured by the HRSD or MADRS in outpatients between:

- SSRIs and TCAs (N= 24; n= 2304; SMD= 0.02; 95% CI, -0.07 to 0.1)
- SSRIs and TCA-related antidepressants (N= 4; n= 226; SMD= -0.06; 95% CI, -0.32 to 0.21)

There is evidence suggesting that there is a statistically significant difference favouring 'third-generation' antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients, but the size of this difference is unlikely to be of clinical significance (N= 9; n= 2096; SMD= 0.13; 95% CI, 0.05 to 0.22).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and MAOIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients.

There is a similar picture in primary care:

There is evidence suggesting that there is no clinically significant difference between SSRIs and other antidepressants on reducing depression symptoms as

measured by the HRSD or MADRS in primary care (N= 4; n= 922; SMD= 0.08; 95% CI, -0.05 to 0.21).

Acceptability and tolerability of treatment

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients leaving treatment early for any reason but the size of this difference is unlikely to be of clinical significance (N= 97; n= 11442; RR= 0.91; 95% CI, 0.87 to 0.96).

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients leaving treatment early due to side effects (N= 89; n= 10898; RR= 0.78; 95% CI, 0.71 to 0.85).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients reporting adverse effects but the size of this difference is unlikely to be of clinical significance (N= 42; n= 5658; RR= 0.94; 95% CI, 0.91 to 0.97).

A sub-analysis against TCAs showed similar results :

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over TCAs on reducing the likelihood of patients leaving treatment early for any reason but the size of this difference is unlikely to be of clinical significance (N= 62; n= 6446; RR= 0.88; 95% CI, 0.82 to 0.93).

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over TCAs on reducing the likelihood of patients leaving treatment early due to side effects (N= 59; n= 6145; RR= 0.69; 95% CI, 0.62 to 0.77)

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over TCAs on the likelihood of patients reporting adverse events but the size of this difference is unlikely to be of clinical significance (N= 17; n= 1846; RR= 0.86; 95% CI, 0.81 to 0.9)

Clinical summary

SSRIs are relatively well tolerated drugs with equal efficacy compared to alternative antidepressants, They are particularly suitable for women who may

respond preferentially to SSRIs (see gender section 8.2.8) and for those with suicidal intent due to their safety in overdose (see section 8.2.6).

8.1.5 Monoamine-oxidase inhibitors (MAOIs)

8.1.5.1 Introduction

Monoamine oxidase inhibitors (MAOIs) exert their therapeutic effect by binding irreversibly to monoamine oxidase, the enzyme responsible for the degeneration of monoamine neurotransmitters such as noradrenaline and serotonin. This results in increased monoamine neurotransmission. The first antidepressant drug synthesised was an irreversible MAOI and drugs in this class have been available in the UK for nearly 50 years.

All MAOIs have the potential to induce hypertensive crisis if tyramine containing foods (tyramine is also metabolised by MAO) are eaten (Merriman, 1999) or drugs that increase monoamine neurotransmission are coprescribed (Livingstone & Livingstone, 1996). These foods and drugs must be avoided for at least 14 days after discontinuing MAOIs. Reversible inhibitors of MAOIs are also available. Moclobemide is the only RIMA licensed in the UK.

Dietary restrictions, potentially serious drug interactions and the availability of safer antidepressants, have led to the irreversible MAOIs being infrequently prescribed in the UK, even in hospitalised patients, However, MAOIs are still widely cited as being the most effective antidepressants for the treatment of atypical depression (see Section 8.2.5).

For this class of drugs the GDG chose to review phenelzine and moclobemide.

8.1.5.2 Moclobemide

Introduction

Moclobemide is a reversible selective inhibitor of monoamine oxidase A (a RIMA) as opposed to the traditional MAOIs that inhibit both MAO A and MAO B irreversibly. It has the advantages over the traditional MAOIs that strict dietary restrictions are not required, drug interactions leading to hypertensive crisis are less problematic and shorter wash out periods are required when switching to other antidepressants. Moclobemide is generally well tolerated as it is associated with a low potential for producing anticholinergic side effects, weight gain and symptomatic postural hypotension. It is not widely prescribed in the UK.

Studies considered for review

Forty-four studies were found in a search of electronic databases with twelve meeting the inclusion criteria set by the GDG and 32 being excluded. Twenty-seven additional studies were identified from other searches undertaken for this

guideline, 14 of which met inclusion criteria with 13 being excluded. Thus a total of 26 studies are included in this review (BAKISH1992, BARRELET1991, BEAUMONT1993, BECKERS1990, BOUGEROL1992, CASCCHIA1984, DUARTE1996, GATTAZ1995, GEERTS1994, GUELFI1992, HEBENSTREIT90, HELL1994, JOUVENT1998, KOCZKAS1989, KRAGHSORENSEN95, LAPIERRE1997, LARSEN1989, LECRUIBEIR1995, NAIR1995, NEWBURN1990, OSE1992, REYNAERT1995, SILVERSTONE94, TANGHE1997, VERSIANI1989A, WILLIAMS1993) providing efficacy data from up to 1742 participants and tolerability data from up to 2149 participants. A total of 45 studies were excluded.

Sixteen studies compared moclobemide with TCAs (BAKSISH1992, BEAUMONT1993, BECKERS1990, GUELFI1992, HEBENSTREIT90, HELL1994, JOUVEN1998, KOCZKAS1989, KRAGHSORENSEN95, LARSEN1989, LECRUBIER1995, NAIR1995, NEWBURN1990, SILVERSTONE94, TANGHE1997, VERSIANI1989), eight with SSRIs (BARRELET1991, BOUGEROL1992, DUARTE1996, GATTAZ1995, GEERTS1994, LAPIERRE1997, REYNAERT1995, WILLIAMS1993) and seven with placebo (BAKISH1992, CASACCHIA1984, LARSEN1989, NAIR 1995, OSE1992, SILVERSTONE1994, VERSIANI1989A).

All included studies were published between 1984 and 1998 and were between four and seven weeks long (mean length = 5.34 weeks). In seven studies participants were classified inpatients, in a further seven outpatients, in two primary care and in ten they were either a mixture of inpatients and outpatients or it the setting was unclear . In one study (NAIR1995) the patients were exclusively older adults (aged 60 – 90). None of the included studies described participants as having depression with atypical features. Participants received between 150mg and 600mg of moclobemide with most receiving at least 300mg.

Data were available to compare moclobemide with amitriptyline, clomipramine, dosulepin, imipramine, nortriptyline, fluoxetine, fluvoxamine and placebo.

Evidence statements for moclobemide compared with placebo

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring moclobemide over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 3; *n* = 490; SMD = -0.6; 95% CI, -1.13 to -0.07).

There is some evidence suggesting that there is a clinically significant difference favouring moclobemide over placebo on increasing the likelihood of achieving at least a 50% reduction in depression symptoms as measured by the HRSD (N = 3; *n* = 606; RR = 0.7; 95% CI, 0.5 to 0.99).

There is insufficient evidence to determine whether there is a clinically significant difference between moclobemide and placebo on increasing the likelihood of achieving remission by the end of treatment (N=2; *n*=111; RR= 0.88; 95% CI, 0.73 to 1.05).

Acceptability and tolerability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between moclobemide and placebo on:

- reducing the likelihood of leaving treatment early for any reason (N = 7; *n* = 819; RR = 0.95; 95% CI, 0.74 to 1.22)
- reducing the likelihood of leaving treatment early due to side effects (N = 6; n = 785; RR = 1.11; 95% CI, 0.6 to 2.04)
- reducing the likelihood of side effects (N = 5; n = 615; RR = 1.12; 95% CI, 0.94 to 1.32).

Evidence statements for moclobemide compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between moclobemide and other antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 13[31]; n = 1222; SMD = 0; 95% CI, -0.12 to 0.11)
- *increasing the likelihood of achieving remission by the end of treatment (N = 5; n = 402; RR = 1; 95% CI, 0.86 to 1.18)*
- increasing the likelihood of achieving at least a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 13; n = 2070; RR = 1.02; 95% CI, 0.93 to 1.13).

Similar results were found in sub-analyses by antidepressant class and setting.

[31] Two studies (DUARTE1996 and TANGHE1997) were removed from this analysis to remove heterogeneity from the dataset, this did not effect the results.

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between moclobemide and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 20; n = 2458; RR = 0.97; 95% CI, 0.85 to 1.11).

Similar results were found in sub-analyses by antidepressant class and setting.

There is strong evidence suggesting that there is a clinically significant difference favouring moclobemide over other antidepressants on reducing the likelihood of leaving treatment due to side effects (N = 18; n = 2292; RR = 0.57; 95% CI, 0.44 to 0.75).

There is evidence suggesting that there is a statistically significant difference favouring moclobemide over other antidepressants on patients reporting side effects but the size of this difference is unlikely to be of clinical significance(N = 12; n = 1472; RR = 0.85; 95% CI, 0.79 to 0.92).

Similar results were found in sub-analyses by setting but not by antidepressant class:

There is evidence suggesting that there is no clinically significant difference between moclobemide and SSRIs on patients reporting side effects (N = 6; *n* = 519; RR = 0.9; 95% CI, 0.79 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference between moclobemide and SSRIs on reducing the likelihood of leaving treatment early due to side effects (N = 6; n = 660; RR = 0.96; 95% CI, 0.59 to 1.57).

There is strong evidence suggesting that there is a clinically significant difference favouring moclobemide over TCAs on reducing the likelihood of leaving treatment due to side effects (N = 12; *n* = 1632; RR = 0.46; 95% CI, 0.34 to 0.64).

There is evidence suggesting that there is a statistically significant difference favouring moclobemide over TCAs on patients reporting side effects but the size of this difference is unlikely to be of clinical importance. (N = 6; *n* = 953; RR = 0.83; 95% CI, 0.76 to 0.91).

Clinical summary

There is some evidence that moclobemide is more effective than placebo, although insufficient evidence of its tolerability and acceptability. There is evidence that it is equally as effective as other antidepressants (TCAs and SSRIs). Whilst moclobemide is equally acceptable and tolerable to patients as SSRIs,

there is strong evidence that patients receiving moclobemide are less likely to leave treatment early due to side effects than patients receiving TCAs.

8.1.5.3 Phenelzine

Introduction

Phenelzine is the best tolerated MAOI. Established side effects include hypotension, drowsiness, dizziness, dry mouth and constipation. It has been associated with hepatotoxicity.

Studies considered for review

Twenty-seven studies were found in a search of electronic databases with nine being included and 18 being excluded by the GDG.

Eight studies compared phenelzine with TCAs (DAVIDSON81, DAVIDSON87, GEORGOTAS86, QUITKIN1990[32], RAFT1981, ROBINSON1983, SWANN1997, VALLEJO87) and one with SSRIs (PANDE1996). These provided efficacy data from up to 634 trial participants and tolerability data from up to 481 participants.

All included studies were published between 1981 and 1997 and were between three and seven weeks long (mean = 5.56 weeks). Participants were described as outpatients in eight studies and as inpatients in the other study (GEORGOTAS86). This study was also the only one in which all participants were 55 years of age or older (mean age 65 years). Studies reported mean doses of between 30 mg and 90 mg of phenelzine. All participants in PANDE1996 and 67% of those in QUITKIN1990were diagnosed with additional atypical features.

Data were available to compare phenelzine with amitriptyline, desipramine[33], imipramine, nortriptyline and fluoxetine.

Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring phenelzine over other antidepressants on:

- achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 2; n= 325; RR= 0.66; 95% CI, 0.52 to 0.83)
- increasing the likelihood of achieving remission by the end of treatment (N= 3; n= 385; RR= 0.77; 95% CI, 0.63 to 0.95).

[32] The data from QUITKIN1990 was supplied as raw individual patient data by the authors to the NCCMH review team.

[33] Not licensed for use in the UK

There is evidence suggesting that there is no clinically significant difference between phenelzine and other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 7; n= 634; SMD= -0.12; 95% CI, -0.28 to 0.04).

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and SSRIs on any efficacy measure, or between phenelzine and TCAs on reducing the likelihood of achieving remission by the end of treatment.

There is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 1; n= 285; RR= 0.66; 95% CI, 0.52 to 0.83).

There is evidence suggesting that there is no clinically significant difference between phenelzine and TCAs on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 6; n= 594; SMD= -0.15; 95% CI, -0.32 to 0.01).

Acceptability and tolerability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and other antidepressants on reducing the likelihood of leaving treatment early for any reason and on reducing the likelihood of leaving treatment early due to side effects.

There is evidence suggesting that there is no clinically significant difference between phenelzine and other antidepressants on patients reporting adverse effects (N= 1; n= 60; RR= 0.97; 95% CI, 0.87 to 1.09).

A sub-analysis by antidepressant class gave similar results.

Clinical summary

There is some evidence suggesting a superior efficacy for response and remission for phenelzine compared to other antidepressants. These findings are probably explained by the high proportion of patients with atypical features in the studies reporting response (71% patients had atypical features) and remission (56% patients had atypical features). A separate review of the pharmacological treatment of atypical depression is provided in Section 8.2.5.

There is no difference in mean endpoint scores between the two groups of treatments in patients with major depressive disorder regardless of additional atypical features. This is also evident in comparisons with TCAs alone. Evidence

from studies comparing phenelzine with SSRIs was too weak to draw any conclusions.

There is insufficient evidence to draw any conclusions on the comparative tolerability of phenelzine against alternative antidepressants.

8.1.6 Third-generation antidepressants[34]

This diverse group of antidepressants was marketed after the SSRIs. The aim was to broaden the mechanism of action beyond serotonin in order to improve efficacy without incurring the side effects or toxicity in overdose associated with the TCAs.

8.1.6.1 Mirtazapine

Mirtazapine is a noradrenaline and specific serotonin antidepressant (NaSSA) which blocks presynaptic alpha 2 receptors on both NA and 5HT neurones and also blocks postsynaptic 5HT2 (less sexual dysfunction but possible worsening of OCD symptoms) and 5HT3 (less nausea) receptors. It can cause weight gain and sedation.

Studies considered for review

Twenty-five studies were found in a search of electronic databases and details of a study in press was provided by Organon (WADE2003). Fifteen were included (although the efficacy data from one of these, WADE2003, was excluded because more than 50% of participants left treatment early) and eleven excluded by the GDG.

Nine studies compared mirtazapine with TCAs and related antidepressants (BREMNER1995, BRUIJN1996, HALIKAS1995, MARTTILA1995, MULLIN1996, RICHOU1995, SMITH1990, VANMOFFAERT95, ZIVKOV1995), five compared it with SSRIs (BENKERT2000, LEINONE1999, SCHATZBERG02, WADE2003, WHEATLEY1998), and one with venlafaxine (GUELFI2001). These provided efficacy data from up to 2,491 trial participants and tolerability date from up to 2,637 participants.

All included studies were published between 1990 and 2003 and were between five and 24 weeks long (mode = 6 weeks). In five studies participants were described as inpatients, in six as outpatients, one was from primary care and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (SCHATZBERG2002) all participants were

[34] Although these are classified 'other antidepressants' by the BNF, to avoid confusion with the guideline's use of 'other antidepressants' to mean **all** other antidepressants, the GDG uses the term 'third-generation antidepressants' to describe this group of drugs.

65 years of age or older). Studies reported mean doses of between 22 mg and 76.2 mg of mirtazapine.

Data were available to compare mirtazapine with amitriptyline, clomipramine, doxepin, imipramine, trazodone, citalopram, fluoxetine, paroxetine and venlafaxine.

Evidence statements

Effect of treatment on efficacy outcomes

There is no difference between the efficacy of mirtazapine and other antidepressants for which comparisons were available:

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on:

- achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N= 14[35]; n= 2440; RR= 0.92; 95% CI, 0.84 to 1.01)
- reducing depression symptoms by the end of treatment as measured by the HRSD or the MADRS (N= 14; n=2314; SMD= -0.03; 95% CI, -0.11 to 0.05).

There is evidence suggesting that there is a statistically significant difference favouring mirtazapine over other antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N= 4; n= 819; RR= 0.91; 95% CI, 0.83 to 0.99).

Similar results were found in sub-analyses by antidepressant class, other than for SSRIs:

There is evidence suggesting that there is a statistically significant difference favouring mirtazapine over SSRIs on reducing depression symptoms by the end of treatment, but the size of this difference is unlikely to be of clinical significance (N= 4; n= 888; SMD= -0.13; 95% CI, -0.27 to 0.00).

Effect of setting on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants:

- on reducing depression symptoms by the end of treatment in inpatients as measured by the HRSD or MADRS (N= 5; n= 854; Random effects: SMD= 0.05; 95% CI, -0.15 to 0.24)

[35] One study (WADE2003) was removed because >50% of participants left the study early.

- on increasing the likelihood of achieving remission in outpatients by the end of treatment (N= 2; n= 387; RR= 0.93; 95% CI, 0.81 to 1.05)
- on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or the MADRS (N= 6; n= 915; SMD= -0.1; 95% CI, -0.23 to 0.03).

In outpatients there is evidence suggesting that there is a statistically significant difference favouring mirtazapine over SSRIs on achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N= 6; n= 957; RR= 0.86; 95% CI, 0.73 to 1).

In inpatients there is insufficient evidence to determine whether there is a clinically significant difference between mirtazapine and other antidepressants on achieving a 50% reduction in depression symptoms or on achieving remission.

No data were available to determine efficacy in patients in primary care.

Acceptability and tolerability of treatment

Mirtazapine appears to be as acceptable to patients as other antidepressants, except that fewer patients leave treatment early due to side effects:

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N= 15; n= 2637; RR= 0.88; 95% CI, 0.78 to 1).

There is strong evidence suggesting that there is a clinically significant difference favouring mirtazapine over other antidepressants on reducing the likelihood of patients leaving treatment early due to side-effects (N= 15; n= 2637; RR= 0.69; 95% CI, 0.55 to 0.87).

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on patients reporting side-effects (N= 6; n= 1253; RR= 0.99; 95% CI, 0.93 to 1.05).

Findings were similar in sub-analyses by setting and class of antidepressant.

Clinical summary

There is no difference between mirtazapine and other antidepressants on any efficacy measure, although in terms of achieving remission, mirtazapine appears to have a statistical though not clinical advantage. In addition, mirtazapine has a

statistical advantage over SSRIs in terms of reducing depression symptoms, but the difference is not clinically important.

However, there is strong evidence that patients taking mirtazapine are less likely to leave treatment early because of side effects, although this is not the case for patients reporting side effects or leaving treatment early for any reason.

Therefore, although mirtazapine is as effective as other antidepressants, it may have an advantage in terms of reducing side effects likely to lead to patients leaving treatment early.

8.1.6.2 Reboxetine

Reboxetine is a relatively selective noradrenergic reuptake inhibitor. Side effects include insomnia, sweating, dizziness, dry mouth and constipation. It may also lower serum potassium (ABPI, 2003). It is not licensed for use in older adults.

Studies considered for review

Eight studies were found in a search of electronic databases, with six (ANDREOLI2002, BAN1998, BERZEWSKI1997, KATONA1999, MASSAN1999, VERSIANI2000B) being included and two excluded.

Three studies compare reboxetine with placebo (ANDREOLI2002, BAN1998, VERSIANI2000B), three with TCAs (BAN1998, BERZEWSKI1997, KATONA1999) and two with SSRIs (ANDREOLI2002, MASSAN1999). These provided efficacy and tolerability data from up to 1,068 trial participants.

All included studies were published between 1997 and 2002 and were between four and eight weeks long (mean = 6.66 weeks). In two studies participants were described as inpatients and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (KATONA1999) all participants were aged 65 years and over). Apart from this study where participants received a dose of 6 mg, doses were between 8 mg and 10 mg of reboxetine.

Data were available to compare reboxetine with desipramine, imipramine, fluoxetine and placebo.

Evidence statements for reboxetine compared with placebo

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring reboxetine over placebo on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 3; n= 479; RR= 0.61; 95% CI, 0.51 to 0.73.

There is some evidence suggesting that there is a clinically significant difference favouring reboxetine over placebo on increasing the likelihood of achieving remission by the end of treatment (N= 1; n= 254; RR= 0.71; 95% CI, 0.59 to 0.87).

Acceptability and tolerability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between reboxetine and placebo on any measure tolerability.

Evidence statements for reboxetine compared with other antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between reboxetine and other antidepressants on:

- achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 5; n= 1068; RR= 0.87; 95% CI, 0.76 to 1.01)
- increasing the likelihood of achieving remission by the end of treatment (N= 4; n= 895; RR= 0.96; 95% CI, 0.84 to 1.09)
- reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 3; n= 618; SMD= -0.09; 95% CI, -0.24 to 0.07).

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between reboxetine and other antidepressants on patients reporting side effects (N= 4; n= 895; RR= 0.98; 95% CI, 0.9 to 1.06).

There is insufficient evidence to determine whether there is a clinically significant difference between reboxetine and other antidepressants on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

8.1.6.3 Clinical summary

Reboxetine is superior to placebo and as effective as other antidepressants in the treatment of depression. There is insufficient evidence to comment on reboxetine's tolerability compared to placebo or alternative antidepressants.

8.1.6.4 Venlafaxine

Venlafaxine was the first of the new generation dual-action antidepressants. It inhibits the reuptake of both serotonin and noradrenaline in the same way as the TCAs. At the standard dose of 75 mg it is an SSRI with dual action emerging at doses of 150 mg and above. At higher doses it also inhibits dopamine reuptake.

Venlafaxine has a broad range of side effects similar to those of the TCAs and SSRIs. It can increase blood pressure at higher doses, is associated with a high incidence of discontinuation symptoms (see section 8.2.8) and is more toxic than the SSRIs in overdose (see section 8.2.9).

8.1.6.5 Studies considered for review

The GDG used an existing review (Smith et al., 2002) as the basis of this review. The original review included 31 studies of which twelve did not meet the inclusion criteria set by the GDG. Fifteen additional studies were identified from new searches, four from another review (Einarson et al., 1999) and details of two unpublished studies were provided by Wyeth Laboratories. All these studies failed to meet the inclusion criteria set by the GDG. Thus a total of 33 studies are excluded from this review with nineteen trials being included (ALVES1999, BENKERT96, CLERC1994, COSTA1998, CUN'HAM94, DIERICK96, GUELFI2001, HACKETT96, LECRUBIE97, MAHAPATRA97, MCPARTLIN98, POIRIER99, RUDOLPH99, SAMUELIAN98, SCHWEIZER94, SIL'STONE99, SMERALDI98, TYLEE1997, TZANAKAKI00). Together these provide tolerability data from up to 3,316 participants and efficacy data from up to 3,328 participants.

All included studies were published between 1994 and 2001 and were between four and twelve weeks long (mean = 8.05 weeks). Three studies were of inpatients, nine of outpatients and three were undertaken in primary care. In the remaining four, it was either not clear from where participants were sourced or they were from mixed sources. In two (MAHAPATRA97, SMERLADI98) participants were aged 64 years and over. Mean HRSD scores at baseline ranged from 22.4 to 29.

Data were available to compare venlafaxine with clomipramine, dosulepin, imipramine, trazodone, fluoxetine, paroxetine and mirtazapine.

Studies reported mean doses equivalent to at least 100 mg of amitriptyline. Three studies (HACKETT96, RUDOLPH1999, SIL'STONE99) used 'extended release' (XR) venlafaxine and the remainder 'immediate release' (IR) venlafaxine. Doses ranged from 75 mg to 365 mg. A sub-analysis was performed by dose of venlafaxine, so that studies achieving a mean dose of less than 150 mg were classified as low dose (ALVES1999, COSTA1998, DIERICK96, LECRUIBIE97, MAHAPATR97, MCPARTLIN98, SAMUELIAN98, SIL'STONE99, SMERALID98, TYLEE1997) and those where the mean dose 150 mg or greater as high dose

(BENKERT96, CLERC1994, GUELFI2001, POIRIER99, RUDOLPH99, SCHWEIZER94, TZANAKAKI00).

8.1.6.6 Evidence statements

Effect of treatment on efficacy

Venlafaxine is no more effective in treating depression than other antidepressants:

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 17; n= 3167; Random effects: RR=0.91;95% CI, 0.81 to 1.03)
- increasing the likelihood of achieving remission as measured by the HRSD (N= 7; n= 1676; Random effects: RR=0.91;95% CI, 0.81 to 1.02).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over other antidepressants on reducing depression symptoms, but the size of this difference is unlikely to be of clinical significance (N= 18; n= 3328; SMD= -0.1; 95% CI, -0.17 to -0.03).

Similar results were found in sub-analyses by class of antidepressant:

There is evidence suggesting that there are statistically significant differences favouring venlafaxine over SSRIs on the following outcomes, but the size of these differences is unlikely to be of clinical significance:

- on achieving a 50% reduction in depression symptoms, (N= 10; n= 2237; RR= 0.9; 95% CI, 0.81 to 1)
- on increasing the likelihood of achieving remission (N= 6; n= 1519; RR= 0.9; 95% CI, 0.83 to 0.98)
- on reducing depression symptoms by the end of treatment (N= 11; n= 2432; SMD= -0.12; 95% CI, -0.2 to -0.04).

There is evidence suggesting that there is no clinically significant difference between venlafaxine and TCAs:

- on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 6; n= 773; RR= 0.92; 95% CI, 0.77 to 1.1)
- on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 6; n= 744; SMD= -0.12; 95% CI, -0.27 to 0.02).

Effect of setting on treatment efficacy

To assess the efficacy of venlafaxine in inpatients, data were available to compare it with imipramine, fluoxetine, and mirtazapine.

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on reducing depression symptoms in inpatients by the end of treatment as measured by the HRSD or MADRS (N= 3; n= 383; Random effects: SMD = -0.04; 95% CI, -0.46 to 0.38).

There is insufficient evidence to determine whether there is a clinically significant difference between venlafaxine and other antidepressants on either achieving a 50% reduction in depression symptoms or on increasing the likelihood of achieving remission.

However, compared with fluoxetine alone, venlafaxine is more effective in inpatients:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over fluoxetine on reducing depression symptoms in inpatients by the end of treatment as measured by the HRSD or MADRS (N= 1; n= 67; SMD= -0.58; 95% CI, -1.07 to -0.09).

Data from studies of venlafaxine in outpatients were available to make comparisons with imipramine, clomipramine, fluoxetine and paroxetine.

Venlafaxine has greater efficacy in outpatients than TCAs:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over TCAs on achieving a 50% reduction in depression symptoms in outpatients as measured by the HRSD (N= 2; n= 248; RR= 0.74; 95% CI, 0.55 to 0.99).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over TCAs on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N= 2; n= 232; SMD= -0.34; 95% CI, -0.6 to -0.08).

This difference is maintained against SSRIs, but is smaller:

In outpatients there is evidence suggesting that there are statistically significant differences favouring venlafaxine over fluoxetine on the following outcomes, but the size of these differences is unlikely to be of clinical significance:

- on reducing depression symptoms by 50% by the end of treatment (N= 5; n= 1235; RR= 0.85; 95% CI, 0.72 to 1)

- on reducing depression symptoms in outpatients by the end of treatment (N= 6; n= 1458; SMD= -0.14; 95% CI, -0.24 to -0.03.

There is evidence suggesting that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving remission in outpatients (N= 2; n= 585; RR= 0.92; 95% CI, 0.79 to 1.07).

Data were available to compare venlafaxine against clomipramine and imipramine in primary care.

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- increasing the likelihood of achieving remission (N= 2; n= 702; RR= 0.96; 95% CI, 0.85 to 1.09)
- reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N= 3; n= 824; SMD= -0.07; 95% CI, -0.21 to 0.06).

Effect of dose on treatment efficacy

Low dose venlafaxine:

There is evidence suggesting that there is no clinically significant difference between venlafaxine (**<150 mg**) and other antidepressants:

- on reducing depression symptoms by 50% (N= 10; n= 2194; RR= 0.92; 95% CI, 0.82 to 1.03)
- on increasing the likelihood of achieving remission (N= 3; n= 1084; RR= 0.97; 95% CI, 0.87 to 1.09)
- on reducing depression symptoms (N= 11; n= 2383; SMD= -0.1; 95% CI, -0.18 to -0.02).

High dose venlafaxine:

There is evidence suggesting that there is no clinically significant difference between venlafaxine (>=150 mg) and other antidepressants:

- on achieving a 50% reduction in depression symptoms (N= 7; n= 973; RR= 0.93; 95% CI, 0.81 to 1.07)
- on reducing depression symptoms (N= 7; n= 945; Random effects: SMD= -0.13; 95% CI, -0.34 to 0.08).

There is insufficient evidence to determine whether there is a clinically significant difference between venlafaxine (>=150 mg) and other antidepressants on increasing the likelihood of achieving remission (N= 4; n= 592; Random effects RR= 0.85; 95% CI, 0.69 to 1.06).

However, when data relating to mirtazapine is removed, there is some evidence suggesting that there is a clinically significant difference favouring venlafaxine

(>=150 **mg**) over other antidepressants (without mirtazapine) on increasing the likelihood of achieving remission (N= 3; n= 435; RR= 0.78; 95% CI, 0.68 to 0.89).

Acceptability and tolerability of treatment

Venlafaxine is as acceptable to patients as other antidepressants:

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- Reducing the likelihood of leaving treatment early for any reason (N= 18; n= 3316; RR= 0.97; 95% CI, 0.87 to 1.09)
- Reducing the likelihood of leaving treatment early due to side-effects (N= 18; n= 3316; RR= 1.05; 95% CI, 0.87 to 1.28)
- Reducing the likelihood of patients reporting adverse events (N= 14; n= 2456; RR= 1.03; 95% CI, 0.98 to 1.08).

However, in a sub-analysis by antidepressant , there is evidence of poorer tolerability compared with fluoxetine:

There is some evidence suggesting that there is a statistically significant difference favouring fluoxetine over venlafaxine on reducing the likelihood of patients leaving treatment early due to side effects (N= 8; n= 1753; RR= 1.36; 95% CI, 1.01 to 1.83).

There is evidence suggesting that there is a statistically significant difference favouring fluoxetine over venlafaxine on reducing the likelihood of patients reporting side effects, but the size of this difference is unlikely to be of clinical significance (N= 7; n= 1550; RR= 1.07; 95% CI, 1 to 1.14).

Acceptability and tolerability of treatment by setting

To assess the efficacy of venlafaxine in inpatients, data were available to compare it with imipramine, fluoxetine and mirtazapine. Heterogeneity was a problem in the meta-analysis assessing the tolerability of venlafaxine against all antidepressants in inpatients. This was because in the study comparing venlafaxine with mirtazapine, fewer participants taking mirtazapine left the study early compared to those taking venlafaxine, whereas this was not the case in other studies. Therefore, the result against TCAs and SSRIs only were considered:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over TCAs and SSRIs on reducing the likelihood of inpatients leaving treatment early (N= 2; n= 235; RR= 0.61; 95% CI, 0.41 to 0.92).

In outpatients venlafaxine is as acceptable as other antidepressants:

There is evidence suggesting that there is no clinically significant difference between Venlafaxine and other antidepressants on:

- Reducing the likelihood of leaving treatment early for any reason (N= 8; n= 1632; RR= 0.97; 95% CI, 0.82 to 1.15)
- Reducing the likelihood of patients reporting side effects (N= 5; n= 1134; RR= 1.05; 95% CI, 0.98 to 1.12).

There is no difference between the tolerability of venlafaxine and other antidepressants in primary care:

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- Reducing the likelihood of leaving treatment early for any reason (N = 3; n = 855; RR = 0.95; 95% CI, 0.76 to 1.17)
- Reducing the likelihood of patients reporting adverse events (N = 2; n = 494; Random effects: RR = 1.06; 95% CI, 0.93 to 1.21).

Acceptability and tolerability of treatment by dose

Low dose venlafaxine

There is evidence suggesting that there is no clinically significant difference between low dose venlafaxine and other antidepressants on reducing the likelihood of leaving treatment early (N= 10; n= 2194; RR= 1.05; 95% CI, 0.91 to 1.22).

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over low dose venlafaxine on reducing the likelihood of reporting side effects but the size of this difference is unlikely to be of clinical significance (N= 9; n= 1833; RR= 1.05; 95% CI, 1 to 1.11).

There is insufficient evidence to determine if there is a clinically significant difference between low dose venlafaxine and other antidepressants on reducing the likelihood of leaving treatment early due to side effects (N= 10; n= 2194; RR= 1.2; 95% CI, 0.94 to 1.53).

In a sub-analysis by class of antidepressant there some evidence suggesting that there is a clinically significant difference favouring SSRIs over low dose venlafaxine on reducing the likelihood of leaving treatment early due to side effects (N= 6; n= 1734; RR= 1.32; 95% CI, 1 to 1.75).

There is strong evidence that there is a clinically significant difference favouring fluoxetine over low dose venlafaxine on reducing the likelihood of leaving treatment early due to side effects (N= 5; n= 1373; RR= 1.69; 95% CI, 1.2 to 2.37).

High dose venlafaxine

There is insufficient evidence to determine whether there is a clinically significant difference between high dose venlafaxine and alternative antidepressants on reducing the likelihood of leaving treatment early or on reducing the likelihood of leaving treatment early due to side effects.

There is evidence suggesting that there is no clinically significant difference between high dose venlafaxine and alternative antidepressants on reducing the likelihood of reporting side effects (N= 5; n= 623; RR= 0.94; 95% CI, 0.84 to 1.06).

In a sub-analysis by antidepressant class there some evidence suggesting that there is a clinically significant difference favouring high dose venlafaxine over TCAs on reducing the likelihood of leaving treatment early (N= 2; n= 313; RR= 0.72; 95% CI, 0.53 to 0.98).

Clinical summary

There are limited clinical benefits favouring venlafaxine against TCAs and SSRIs (but not mirtazapine). Therefore the evidence does not indicate the routine use of venlafaxine (particularly in light of potential adverse effects), although its use may be justified in individual cases (see below).

In inpatients, there is limited evidence that venlafaxine is as effective as imipramine and more effective than fluoxetine with evidence of fewer patients leaving treatment early. There is some evidence that higher dose venlafaxine increases the likelihood of remission compared to TCAs and SSRIs (but not mirtazapine) and that in the populations studied high dose venlafaxine is as well tolerated as most other antidepressants and better than TCAs.

In outpatients, overall there is a small, but not clinically significant benefit compared with other antidepressants, except against TCAs where there is some evidence of better efficacy with venlafaxine. There is evidence that more patients leave treatment early because of side effects with venlafaxine compared with fluoxetine, although the difference is not statistically significant. Venlafaxine has a small clinical advantage in outpatients with moderate to severe depression, who fail to respond to SSRIs or who fail to tolerate TCAs.

In low dose, there is no evidence of a clinical advantage for venlafaxine in comparison to SSRIs. In addition, there is strong evidence of an increased

likelihood of patients leaving treatment early due to side effects when compared to fluoxetine.

8.1.7 St John's wort

St John's wort, an extract of the plant Hypericum perforatum, has been used for centuries for medicinal purposes including the treatment of depression. It is not licensed as a medicine in the UK but can be bought 'over the counter' from health food shops, herbalists and community pharmacies. Many different branded preparations are available. St John's wort is licensed in Germany for the treatment of depression.

St John's wort is known to contain at least ten constituents or groups of components that may contribute to its pharmacological effects (Linde & Mulrow, 2003), but its exact mode of action is unknown. These include naphthodianthrons (f.e. hypericins), flavonoids (f.e. quercetin), xanthons and biflavonoids (Wagner, 1994). In common with all herbal preparations, the quantity and proportions of each constituent varies between batches. Most commercial products are standardised with respect to hypericin content but it is not known if this is the only active component. Individual brands or batches of the same brand may therefore not be therapeutically equivalent. Many clinically significant drug interactions have been reported (Committee on Safety of Medicines, 2000). St John's wort may also cause photosensitivity.

8.1.7.1 Studies considered for review

Forty studies were found in a search of electronic databases, with 19 being included and 21 being excluded by the GDG.

Ten studies were available for a comparison with placebo (DAVIDSON02, HANSGEN1996, KALB2001, LAAKMANN98, LECRUBIER02, PHILIPP99, SCHARDER98, SHELTON2001, WITTE1995); four studies for a comparison with TCAs (PHILIPP99, WOELK2000, BERGMANN1993, WHEATLEY1997); one with TCA-related antidepressants (HARRER94), and six studies for a comparison with SSRIs (BEHNKE2002, BRENNER00, DAVIDSON02, HARRER99, SCHRADER00, VANGURP02). (NB DAVIDSON02 and PHILIPP99 are 3-arm trials.) Data from up to 1,520 participants were available from studies comparing St John's wort with placebo, and from up to 1,629 participants were available from comparison with antidepressants.

All included studies were published between 1993 and 2002 and were between four and twelve weeks long (mean number of weeks = 6.47). In sixteen studies participants were described as outpatients and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In

one (HARRER99) all participants were aged 60 years and over. All participants had either moderate or severe depression.

It is very difficult to assess the exact content of the preparation of St John's wort used in included studies so no study was excluded on grounds of inadequate dose. Included studies described the following range of preparations:

- 2 x 150 mg (300 mg) @ 0.450-0.495 mg total hypericin per tablet
- 900 mg LI 160
- 4 x 200 mg (800 mg) LoHyp-57: drug extract ratio 5-7:1
- 3 x 300 mg (900 mg) WS5572: drug extract ratio 2.5-5:1, 5% hyperforin
- 3 x 300 mg (900 mg) WS5573: 0.5% hyperforin
- 3 x 300 mg (900 mg) WS5570: 0.12-0.28% hypericin
- 3 x 350 mg (1050 mg) STEI 300: 0.2-0.3% hypericin, 2-3% hyperforin
- 2 x 200 mg (500 mg) ZE117: 0.5 mg hypericin
- 3 to 6 x 300 mg (900 mg to 1800 mg) @ 0.3% hypericum
- 3 x 300 mg (900 mg) LI 160 = 720-960µg hypericin
- 2 x 250 mg (500 mg) ZE117: 0.2% hypericin
- 900 mg to 1500 mg LI 160: standardised to 0.12-0.28% hypericin
- 4 x 125 mg (500 mg) Neuroplant
- 200-240 mg Psychotonin forte
- 3 x 30 drops Psychotonin (500 mg)
- 3 x 30 drops Hyperforat: 0.6 mg hypericin

In addition six studies with low doses of standard antidepressants were also included.

8.1.7.2 Evidence statements for St John's wort compared with placebo

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring St John's wort over placebo on achieving a 50% reduction in depression symptoms as measured by the HRSD:

- In the dataset as a whole (N= 6[36]; n= 995; RR= 0.79; 95% CI, 0.71 to 0.88)
- In moderate depression (N= 1; n= 162; RR= 0.64; 95% CI, 0.51 to 0.79)
- In severe depression (N= 5[37]; n= 898; RR= 0.81; 95% CI, 0.72 to 0.9).

[36] Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the dataset.

[37] Two studies (DAVIDSON02, HANGSEN1996) were removed from the meta-analysis to remove heterogeneity from the dataset

There is insufficient evidence to determine if there is a clinically significant difference between St John's wort and placebo on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N= 3; n= 804; Random effects: RR= 0.80; 95% CI, 0.53 to 1.22).

There is evidence suggesting that there is a statistically significant difference favouring St John's wort over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance:

- In the dataset as a whole (N= 6[38]; n= 1031; SMD= -0.35; 95% CI, -0.47 to -0.22)
- In severe depression (N= 5[39]; n= 891; SMD= -0.34; 95% CI, -0.47 to -0.2).

However, In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John's wort over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD (N= 2; n= 299; Random effects: SMD= -0.71; 95% CI, -1.28 to -0.13).

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between St John's wort and placebo on reducing the likelihood of patients leaving treatment early for any reason (N= 8; n= 1472; RR= 0.96; 95% CI, 0.74 to 1.25).

There is insufficient evidence to determine if there is a clinically significant difference between St John's wort and placebo on reducing the likelihood of patients leaving treatment early due to adverse effects (N= 5; n= 1127; RR= 0.88; 95% CI, 0.32 to 2.41).

There is evidence suggesting that there is no clinically significant difference between St John's wort and placebo on reducing the likelihood of patients reporting adverse effects (N= 7; n= 1106; RR= 0.89; 95% CI, 0.72 to 1.1).

8.1.7.3 Evidence statements for St John's wort compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between St John's wort and antidepressants on:

[38] Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the dataset.

[39] Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the dataset.

- Achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 10; n= 1612; Random effects: RR= 1.03; 95% CI, 0.87 to 1.22)
- Increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N= 1; n= 224; RR= 1.01; 95% CI, 0.87 to 1.17)
- Reducing depression symptoms by the end of treatment as measured by the HRSD (N= 9; n= 1168; SMD= -0.02; 95% CI, -0.13 to 0.1).

A sub-analyses by severity found no difference in these results except for response rates in those with moderate depression:

In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John's wort over antidepressants on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 3; n= 481; RR= 0.77; 95% CI, 0.62 to 0.95)

Sub-analyses by antidepressant class and by antidepressant dose (therapeutic versus low-dose) found similar results.

A sub-analyses combining severity and dose also found similar results apart from for response rates in severe depression:

In severe depression there is some evidence suggesting that there is a clinically significant difference favouring low dose antidepressants over St John's wort on achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 4; n= 521; RR= 1.2; 95% CI, 1 to 1.44).

Acceptability and tolerability of treatment

With regard to reducing the likelihood of patients leaving treatment early for any reason, there is insufficient evidence to determine a difference between St John's wort and either all antidepressants or low-dose antidepressants. However, there is some evidence suggesting that there is a clinically significant difference favouring St John's wort over antidepressants given at therapeutic doses (N= 5; n= 1011; RR= 0.69; 95% CI, 0.47 to 1).

There is strong evidence suggesting that there is a clinically significant difference favouring St John's wort over antidepressants on:

- reducing the likelihood of patients leaving treatment early due to side effects (N= 10; n= 1629; RR= 0.39; 95% CI, 0.26 to 0.6)
- reducing the likelihood of patients reporting adverse effects (N= 8; n= 1358; RR= 0.65; 95% CI, 0.57 to 0.75).

8.1.7.4 Clinical summary

St John's wort is more effective than placebo on achieving response in both moderate and severe depression, and on reducing depression symptoms in moderate depression.

There appears to be no difference between St John's wort and other antidepressants, other than in moderate depression where it is better at achieving response and in severe depression where it is less effective than than low-dose antidepressants in acheiving response.

However, St John's wort appears as acceptable as placebo, and more acceptable than antidepressants, particularly TCAs, with fewer people leaving treatment early due to side effects and reporting adverse events.

8.1.8 Recommendations for the use of individual drugs in the treatment of depression

8.1.8.1 Antidepressants are not recommended for the initial treatment of mild depression because the risk-benefit ratio is poor. (C)

8.1.8.2 For patients with mild depression, which is persisting after other interventions, and those whose depression is associated with psychosocial and medical problems, the use of an antidepressant may be considered. (C)

8.1.8.3 Where patients with a past history of moderate or severe depression present with mild depression, consideration should be given to the use of an antidepressant. (C)

8.1.8.4 Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment and the need to take medication as prescribed. Written information appropriate to the patient's needs should be made available. (GPP)

8.1.8.5 When an antidepressant is to be prescribed in routine care, it should be an SSRI because they are as effective as tricyclic antidepressants and their use is less likely to be discontinued due to side effects. (A)

8.1.8.6 When prescribing an SSRI, consideration should be given to using a product in a generic form. Fluoxetine, for example, would be a reasonable choice because it is associated with fewer discontinuation

symptoms because it has a longer half-life than other SSRIs. However, it is associated with a high propensity for drug interactions. (C)

8.1.8.7 If a depressed patient being treated with an SSRI develops increased agitation early in treatment provide appropriate information, and if the patient prefers, either change to a different antidepressant or consider a brief period of concomitant treatment with a benzodiazepine followed by a clinical review within 2 weeks. (C)

8.1.8.8 When venlafaxine is prescribed, practitioners and patients need to be aware of:

- Its higher cost and - at low dose - the increased likelihood of patients stopping treatment due to side effects compared with equally effective SSRIs. (A)

- Its high propensity for discontinuation symptoms if stopped abruptly and its toxicity in overdose. (C)

8.1.8.9 Moclobemide is an alternative antidepressant to consider but prescribers need to be aware of the need to wash out previously prescribed antidepressants. (A)

8.1.8.10 Reboxetine is another antidepressant to consider but practitioners need to be aware of its relative lack of data on side effects and careful monitoring is advised. (B)

8.1.8.11 Tricyclics are another option to consider but practitioners need to be aware of their poorer tolerability compared with other equally effective antidepressants, the increased risk of cardiotoxicity and their toxicity in overdose. (B)

8.1.8.12 Despite evidence supporting the tolerability of dosulepin, relative to other antidepressants, this is outweighed by the increased cardiac risk and toxicity in overdose, and therefore it should not be initiated routinely. (C)

8.1.8.13 When a patient's depression fails to respond to the first antidepressant prescribed check that the drug has been taken regularly and in the prescribed dose. (GPP)

8.1.8.14 If response to a standard dose of an antidepressant is inadequate, and there are no significant side effects, an increase in dose within BNF dosage limits should be considered. (C)

8.1.8.15 If an antidepressant has not been effective and, after consideration of a range of other treatment options, the decision is to offer a further course of antidepressants, then switch to another single antidepressant. **(C)**

8.1.8.16 The choice of second antidepressant should take into account the patient's symptom profile. Reasonable choices for a second antidepressant include a different SSRI or mirtazapine but consideration may also be given to other alternatives including moclobemide, reboxetine, tricyclics and venlafaxine. **(B)**

8.1.8.17 When prescribed mirtazapine, patients need to be advised about its propensity to cause sedation and weight gain. (A)

8.1.8.18 Prescribers should be aware of the need for gradual and modest incremental increases of dose, of interactions between antidepressants and the risk of serotonin syndrome when combinations of serotonergic

antidepressants are prescribed when switching from one antidepressant to another. (C)

8.1.8.19 Where a tricyclic is chosen as an antidepressant, lofrepramine is a reasonable choice because of its relative lack of cardiotoxicity. (C)

8.1.8.20 Treatments such as combined antidepressants, lithium augmentation of antidepressants and phenelzine, should not be routinely initiated in primary care. (GPP)

8.1.8.21 Although there is evidence that St John's wort may be of benefit in mild or moderate depression, healthcare professionals should be aware that it is not a licensed product and therefore should not prescribe it. (GPP)

8.1.8.22 Patients who are taking St John's wort should be informed of the different potencies of the preparations available and the uncertainty that arises from this. They should also be informed of the interactions of St John's wort with other drugs. (C)

8.2 Factors that influence choice of antidepressant

8.2.1 Introduction

Whilst the previous section reviewed the relative efficacy of different antidepressants, this section looks at factors that may affect the choice of antidepressant.

The section reviews the following:

- The pharmacological management of depression in older adults
- The effect of gender on the pharmacological management of depression
- The pharmacological management of psychotic depression
- The pharmacological management of atypical depression
- The pharmacological management of relapse prevention
- Dosage issues
- Antidepressant discontinuation symptoms
- The cardiotoxicity of antidepressants
- Depression, suicide and antidepressants

8.2.2 The pharmacological management of depression in older adults

8.2.2.1 Introduction

Depression is the most common mental health problem of later life affecting approximately 15% of older people (Beekman et al, 1999). Untreated it shortens life, increases healthcare costs, as well as adding to disability from medical illnesses, and is the leading cause of suicide amongst older people (Lebowitz et al, 1997). Most depression in older adults is treated in primary care (Plummer et al., 1997) but there is evidence of poor detection (ibid.) and sub-optimal treatment (Iliffe et al., 1991). In this population the monitoring of self harm is particularly important. It is also very important to educate the patient and caregivers about depression and involve them in treatment decisions. Older adults are at risk of co-existing physical disorder, sensory deficits and other handicaps and therefore medication needs to be carefully monitored in these groups.

The efficacy of antidepressants in older adults has been summarised in a Cochrane systematic review (Wilson et al, 2001). There is some evidence that older people take longer to recover than younger adults and adverse events need to be carefully monitored for since they might substantially effect function in a vulnerable individual. There are a variety of potential differences in older adults in terms of absorption and metabolism of drugs and increased potential for interaction with other drugs. The maxim is therefore to start low and increase slowly but it is clear much more research involving older depressed patients is required on this and other points.

It was possible to review the following pharmacological strategies for the treatment of depression in older adults:

- Use of individual antidepressants: amitriptyline, TCAs as a group, SSRIs, phenelzine, mirtazapine, venlafaxine and St John's wort (studies were also available for reboxetine but, since this drug is not licensed for the treatment of depression in older adults, this drug is not reviewed)
- Augmentation of an antidepressant with lithium
- Strategies for relapse prevention

8.2.2.2 Use of individual antidepressants in the treatment of depression in older adults

Studies considered for review

This review brings together studies from other reviews undertaken for this guideline where more than 80% of study participants were aged 65 years and over. A separate systematic search of the literature was not undertaken and,

therefore, studies undertaken with elderly populations using drugs not reviewed for this guideline are not included.

In all fifteen studies from other reviews of individual antidepressants were at least 60 years of age (COHN1990, DORMAN1992, FEIGHNER1985A, GEORGOTAS86, GERETSEGGER95, GUILLIBERT89, HARRER99, HUTCHINGSON92, LAPIA1992, MAHAPATR97, PELICIER1993, PHANJOO1991, RAHMAN1991, SCHATZBERT02, SMERALDI98). Ten studies were sourced from the review of SSRIs, two from venlafaxine and one from each from mirtazapine, phenelzine and St John's wort. Studies were included provided the mean dose achieved was at least half the 'standard' adult dose. Efficacy data were available from up to 1,083 patients, and tolerability data from up to 1,620 patients.

All included studies were published between 1985 and 2003. Two were classified inpatient, eight outpatient and one primary care. In four participants were either from mixed sources or it was either not possible determine the source.

8.2.2.3 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms in elderly patients:

- between amitriptyline and paroxetine (N= 2; n= 126; SMD= -0.1; 95% CI, -0.46 to 0.27)
- between SSRIs and alternative antidepressants (N= 8; n= 602; SMD= -0.01; 95% CI, -0.17 to 0.15)
- between venlafaxine and TCAs (N= 2; n= 202; SMD= 0.02; 95% CI, -0.26 to 0.29)
- between alternative antidepressants and TCAs (N=6, n=443; SMD= 0.00; 95% CI, -0.19 to 0.)
- St John's wort and fluoxetine (N= 1; n= 149; SMD= -0.04; 95% CI, -0.36 to 0.28)
- mirtazapine and paroxetine (N=1, n=254; SMD= -0.12; 95% CI, -0.37 to 0.13).

There is insufficient evidence to determine if there is a clinically significant difference in elderly patients on achieving a 50% reduction in depression symptoms:

- between amitriptyline and paroxetine
- between venlafaxine and TCAs
- between alternative antidepressants and TCAs
- between St John's Wort and fluoxetine
- between mirtazapine and paroxetine.

There is evidence suggesting that there is no clinically significant difference between mirtazapine and paroxetine on increasing the likelihood of achieving remission in elderly patients (N=1, n=254; RR= 0.87; 95% CI, 0.73 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference in elderly patients on increasing the likelihood of achieving remission:

- between phenelzine and nortriptyline
- alternative antidepressants and TCAs.

Acceptability and tolerability of treatment

There some evidence suggesting that there is a clinically significant difference favouring paroxetine over amitriptyline on reducing the likelihood of elderly patients reporting adverse effects (N= 1; n= 90; RR= 0.55; 95% CI, 0.35 to 0.86).

There is some evidence suggesting that there is a clinically significant difference favouring mirtazapine over paroxetine on reducing the likelihood of elderly patients leaving treatment early due to side effects (N=1, n=254; RR= 0.57; 95% CI, 0.34 to 0.94).

There is evidence suggesting that there is no clinically significant difference between alternative antidepressants and TCAs on reducing the likelihood of elderly patients reporting adverse effects (N=7, n=581; RR= 0.89; 95% CI, 0.79 to 1.02)).

There is evidence suggesting that there is no clinically significant difference on reducing the likelihood of elderly patients leaving treatment early:

- between amitriptyline and SSRIs(N= 3; n= 422; RR= 0.89; 95% CI, 0.7 to 1.12)
- between SSRIs and alternative antidepressants (N= 10; n= 1,115; RR= 0.96; 95% CI, 0.82 to 1.13)
- between antidepressants and TCAs (N= 10; n= 1058; RR= 0.97; 95% CI, 0.83 to 1.13).

There is evidence suggesting that there is no clinically significant difference between SSRIs and alternative antidepressants on reducing the likelihood of elderly patients leaving treatment early due to side effects (N= 10; n= 1,154; RR= 1; 95% CI, 0.81 to 1.23).

There is evidence suggesting that there is no clinically significant difference on reducing the likelihood of elderly patients reporting adverse events:

- between SSRIs and alternative antidepressants(N= 8; n= 717; RR= 0.95; 95% CI, 0.85 to 1.05)
- between phenelzine and nortriptyline (N= 1; n= 60; RR= 0.97; 95% CI, 0.87 to 1.09
- between mirtazapine and paroxetine (N=1, n=254; RR= 0.97; 95% CI, 0.86 to 1.09).

There is insufficient evidence to determine if there is a clinically significant difference between other drug comparison on other tolerability measures.

Effect of setting on treatment efficacy and tolerability

There is evidence suggesting that there is no clinically significant difference between SSRIs and alternative antidepressants on reducing depression symptoms in elderly inpatients (N= 2; n= 95; SMD= -0.07; 95% CI, -0.48 to 0.33).

There is insufficient evidence to determine any difference on any efficacy measure in outpatients or patients in primary care.

There is insufficient evidence to determine any difference on tolerability measures for any patient setting.

8.2.2.4 Augmentation of an antidepressant with lithium in the elderly

Studies considered for review

In the review of lithium augmentation all participants in one study (JENSEN1992) were aged 65 years or over. This was of inpatients, and compared nortriptyline (25-100mg, median=75mg) plus lithium with nortriptyline (50-100mg, median =75mg) and placebo.

Evidence statements

Effect of treatment on efficacy outcomes

There some evidence suggesting that there is a clinically significant difference favouring nortriptyline alone over nortriptyline plus lithium on increasing the likelihood of achieving remission in elderly patients (N= 1; n= 44; RR= 2.28; 95% CI, 1.09 to 4.78).

Acceptability and tolerability of treatment

There some evidence suggesting that there is a clinically significant difference favouring nortriptyline alone over nortriptyline plus lithium on reducing the likelihood of elderly patients leaving treatment early (N= 1; n= 44; RR= 5.02; 95% CI, 1.26 to 20.07).

There is insufficient evidence to determine if there is a clinically significant difference between nortriptyline plus lithium and nortriptyline alone on reducing the likelihood of elderly patients leaving treatment early due to side effects (N= 1; n= 44; RR= 5.48; 95% CI, 0.72 to 41.82).

8.2.2.5 Relapse prevention in the elderly

Studies considered for review

Five studies looked at relapse prevention in older adults (all at least 65 years of age or with a mean age of 65 years) (ALEXOPOULOS2000, COOK1986, GEORGOTAS1989, KLYSNER2002, WILSON2003), one in patients in primary care (WILSON2003) and four in outpatients (ALEXOPOULOS00, KLYSNER2002, COOK1986, GEORGOTAS1989).

Evidence statements

In an analysis of all available data comparing maintenance treatment with an antidepressant with placebo there is strong evidence suggesting that there is a clinically significant difference favouring continuing treatment with antidepressants over discontinuing antidepressants on reducing the likelihood of relapse in elderly patients (N= 5; n= 345; RR= 0.55; 95% CI, 0.43 to 0.71).

Where there was sufficient evidence, there was little difference in the results of sub-analyses by length of pre-randomisation treatment or by post-randomisation treatment, by a combination of these factors, or between results for SSRIs and TCAs analysed separately. Nor was any difference found for patients in their first episode or for those with previous episodes.

Clinical summary

There is no difference in the efficacy of the various antidepressants for which studies have been undertaken in the elderly. There is also little evidence of differences in acceptability, apart from between paroxetine and amitriptyline, where fewer patients taking paroxetine report adverse events. There is little evidence that there is a difference by patient setting.

With regard to augmenting an antidepressant with lithium, elderly patients appear to be more likely to achieve remission without the addition of lithium. These patients are also less likely to leave treatment early.

It appears to be worthwhile continuing pharmacological treatment in elderly patients with multiple depressive episodes in order to avoid relapse.

These results are similar to those found in the reviews of studies for all adult patients elsewhere in this guideline.

8.2.2.6 Recommendations for the pharmacological management of the elderly

8.2.2.6.1 For older adults with depression, antidepressant treatment should be given at an age-appropriate dose for a minimum of 6 weeks before treatment is considered to be ineffective. In those who have made a partial response within this period treatment should be continued for a further 6 weeks. (C)

8.2.2.6.2 Healthcare professionals should be aware of the increased frequency of drug interactions when prescribing an antidepressant to older adults who are taking other medications. (GPP)

8.2.2.6.3 When prescribing antidepressants, in particular tricyclics, for older adults with depression, careful monitoring for side effects should be undertaken. (C)

8.2.2.6.4 Depression in the context of dementia should be treated in the same way as depression in other older adults. (C)

8.2.2.6.5 Healthcare professionals should be aware that depression responds to antidepressants even in the presence of dementia. (C)

8.2.2.7 Research recommendations

Further research is needed on all aspects of the pharmacological treatment of depression in the elderly, in particular, in those over 80 years of age. There is an especial need for research evidence on optimum treatment and maintenance doses for these populations.

8.2.3 The effect of gender on the pharmacological management of depression

8.2.3.1 Introduction

Although the female preponderance in the prevalence of unipolar depression has been well established (Weissman et al., 1993) little attention has been paid to gender differences in treatment response to antidepressant medication. A meta-analysis of 35 studies published between 1957 and 1991 that reported imipramine response rates separately by gender reported that men responded more favourably to imipramine than did women (Hamilton et al., 1996). Kornstein et al. (2000) in a study of 635 patients showed a trend towards men responding more positively to imipramine compared with sertraline (RR= 0.76, 95% CIs 0.55 to 1.02), whilst there was some evidence that women responded more positively

to sertraline rather than imipramine (RR= 0.80, 95% CIs 0.66 to 0.98). In this study women taking imipramine were more likely to leave the study early compared to those taking sertraline (n=400; RR= 0.53, 95% CIs 0.35 to 0.80); this difference was not present for men. In a study which compared tricyclic antidepressants and monoamine oxidase inhibitors found that in patients with atypical depression and associated panic attacks, women showed a more favourable response to MAOIs and men to tricyclic antidepressants (Davison and Pelton, 1986). These differential response patterns suggest that gender should be considered when making treatment decisions. There are a number of possible mechanisms whereby gender may influence treatment response. Drugs with effects on the serotonergic system may be relevant for younger women since serotonergic agents have demonstrated efficacy in disorders such as premenstrual dysphoric disorder (Thase et al, 1997). Secondly the presence of atypical depression may modify treatment responsivity and women are more likely to present with atypical depressive symptoms (Kornstein, 1997). Another explanation is that female reproductive hormones may play a permissive or inhibitory role in antidepressant activity. For example oestrogen may enhance serotonergic activity (Halbreich et al, 1995).

8.2.3.2 Data reviewed

The data used in this section comprised individual patient data from published trials undertaken by Quitkin and colleagues and supplied by them to the NCCMH review team. This is therefore not a systematic review. The data included gender, diagnosis, study drug, and baseline and endpoint HRSD scores. Patient data was included only from those diagnosed with major depressive disorder regardless of additional diagnoses. The study drugs included were TCAs and phenelzine. These were compared with placebo and with each other. The data were analysed for men and women separately.

8.2.3.3 Evidence statements for TCAs versus placebo

In men there is evidence suggesting that there is no clinically significant difference between TCAs and placebo on achieving a 50% reduction in depression symptoms (n= 157; RR= 0.89; 95% CI, 0.75 to 1.06).

In women there is some evidence suggesting that there is a clinically significant difference favouring TCA over placebo on achieving a 50% reduction in reducing depression symptoms (n= 246; RR= 0.82; 95% CI, 0.7 to 0.95).

In men there is insufficient evidence to determine whether there is a clinically significant difference between TCAs and placebo on increasing the likelihood of achieving remission (n= 157; RR= 0.87; 95% CI, 0.73 to 1.04).

In women there is evidence suggesting that there is a statistically significant difference favouring TCAs over placebo on increasing the likelihood of achieving remission in women, but the size of this difference is unlikely to be of clinical significance (n= 246; RR= 0.84; 95% CI, 0.73 to 0.97).

In men there is evidence suggesting that there is no clinically significant difference between TCAs and placebo on reducing depression symptoms (n= 157; WMD= -1.29; 95% CI, -2.87 to 0.28).

In women there is evidence suggesting that there is a statistically significant difference favouring TCAs over placebo on reducing depression symptoms, but the size of this difference is unlikely to be of clinical significance (n= 246; WMD= -1.62; 95% CI, -2.84 to -0.4).

8.2.3.4 Evidence statements for phenelzine versus placebo

Women do slightly better on phenelzine compared to placebo than men:

In men there is strong evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on achieving a 50% reduction in depression symptoms in men (n= 134; RR= 0.64; 95% CI, 0.48 to 0.84)

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on achieving a 50% reduction in depression symptoms in women (n= 188; Random effects RR= 0.53; 95% CI, 0.31 to 0.91)

In men there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on:

- increasing the likelihood of achieving remission (n= 134; RR= 0.66; 95% CI, 0.5 to 0.86)
- reducing depression symptoms (n= 134; Random effects: WMD= -5.02; 95% CI, --9.68 to –0.35).

In women there is strong evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on reducing depression symptoms (n= 188; WMD= -6.27; 95% CI, -8.15 to -4.4).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on increasing the likelihood of achieving remission (n= 188; Random effects: RR= 0.47; 95% CI, 0.25 to 0.89).

8.2.3.5 Evidence statements for TCAs versus phenelzine

It appears that women may do better on phenelzine than on TCAs compared to men:

In men there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on achieving a 50% reduction in depression symptoms (n= 131; RR= 1.41; 95% CI, 1.05 to 1.9).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs in achieving a 50% reduction in depression symptoms (n= 154; Random effects RR= 1.52; 95% CI, 0.92 to 2.52).

In men there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving remission (n= 131; RR= 1.32; 95% CI, 1 to 1.75).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving remission in women (n= 154; Random effects RR= 1.76; 95% CI, 1.01 to 3).

In men there is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and TCAs on reducing depression symptoms (n= 131; Random effects WMD= 3.21; 95% CI, -0.14 to 6.57).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on reducing depression symptoms (n= 154; WMD= 4.43; 95% CI, 2.47 to 6.4).

8.2.3.6 Clinical summary

In patients with chronic depression, women respond better to SSRIs than to TCAs, whereas there is some indication that men may respond better to TCAs. Imipramine was associated with less tolerability than sertraline in women; this was not the case for men.

Women treated in a specialist tertiary depression centre, the majority of whom have atypical depression, respond better to treatment with antidepressants than men, particularly to phenelzine. Men with this disorder treated in the same setting do not respond to TCAs, but do respond to phenelzine, although to a lesser extent than women.

Note that all this data comes from specific populations rather than a representative sample of people with major depressive disorder.

8.2.3.7 Recommendations for gender

8.2.3.7.1 When determining which antidepressants to prescribe female patients, their poorer toleration of imipramine should be considered. (B)

8.2.3.7.2 In female patients with atypical features consideration should be given to prescribing an MAOI in those who have not responded to, or who cannot tolerate, an SSRI. (C)

8.2.3.7.3 In male patients with chronic depression who have not responded to an SSRI, consideration should be given to a tricyclic antidepressant, because men tolerate the side effects of tricyclic antidepressants reasonably well. (C)

8.2.4 The pharmacological management of psychotic depression

8.2.4.1 Introduction

Major depression with psychotic features is a disorder with considerable morbidity and mortality. In the epidemiologic catchment area study (Johnson et al 1991) 14.7% of patients who met the criteria for major depression had a history of psychotic features. The prevalence is higher in samples of elderly patients. The disorder is often not diagnosed accurately because the psychosis may be subtle, intermittent or concealed. There has been a longstanding debate as to whether major depression with psychotic features is a distinct syndrome or represents a more severe depressive subtype. The weight of evidence suggests that severity alone does not account for the differences in symptoms, biological features and treatment response (Rothschild, 2003). The systematic study of major depression with psychotic features has been limited by the fact that the disorder does not exist as a distinct diagnostic subtype in DSM IV and because of the difficulties in enrolling such patients in research studies. As a result there are few controlled studies on the acute treatment of psychotic depression and no long-term maintenance studies. There is some evidence that patients with major depression with psychotic features exhibit more frequent relapses or recurrences than patients with non-psychotic depression though not all studies are in agreement (see Rothschild, 2003). Patients with major depression with psychotic features demonstrate more severe psychomotor disturbance more frequently than patients without psychosis.

8.2.4.2 Studies considered for review

Twenty studies were found in a search of electronic databases, six of which met the inclusion criteria set by the GDG (ANTON1990, BELLINI1994, MULSANT2001, SPIKER1985, ZANARDI1996, ZANARDI2000) and fourteen of which did not, mainly because too many participants had been diagnosed with bipolar depression and therefore fell outside the inclusion criteria set by the GDG.

Five studies (ANTON1990, BELLINI1994, MULSANT2001, SPIKER1985) looked at augmenting an antidepressant with an antipsychotic and two (ZANARDI1996,

ZANARDI2000) compared a single antidepressant to another. The following comparisons were possible:

- Amitriptyline plus perphenazine versus amoxapine
- Nortriptyline plus perphenazine versus nortriptyline plus placebo
- Amitriptyline plus perphenazine versus amitriptyline
- Desipramine plus haloperidol versus desipramine plus placebo[40]
- Fluvoxamine plus haloperidol versus fluvoxamine plus placebo[40]
- Paroxetine versus sertraline
- Fluvoxamine versus venlafaxine.

In comparisons involving antipsychotic augmentation efficacy data were available from up to 103 participants and tolerability data from up to 87 participants. In comparisons comparing single antidepressants both efficacy and tolerability data were available from up to 60 participants. All included studies were published between 1985 and 2001 and were between four days and sixteen weeks (mean = 7.17 weeks).

All studies were of inpatients, and in one all patients were at least 50 years of age (mean 71) (MULSANT2001). Participants had a diagnosis of major depressive disorder with psychotic features. In two studies (ANTON1990, ZANARDI2000) up to 25% (the limit allowed in the inclusion criteria set by the GDG is 15%) of participants were diagnosed with bipolar disorder. Two sets of analyses were performed including and excluding these two studies. There was no difference in results, so statements from the analysis excluding these studies are presented below.

8.2.4.3 Evidence statements

Effect of treatment on efficacy

There some evidence suggesting that there is a clinically significant difference favouring sertraline over paroxetine on increasing the likelihood of achieving remission as measured by the HRSD (N= 1; n= 32; RR= 2.83; 95% CI, 1.28 to 6.25).

There is insufficient evidence on any efficacy measure to determine if there is a clinically significant difference between TCA plus an antipsychotic and either amoxapine or a TCA.

[40] Four-armed trial (BELLINI1994)

Acceptability and tolerability of treatment

There is insufficient evidence to determine if there is a clinically significant difference on the acceptability of treatment:

- between perphenazine augmentation of a tricyclic antidepressant and tricyclic monotherapy
- between paroxetine and sertraline.

8.2.4.4 Clinical summary

There is no good quality evidence for pharmacological treatments of psychotic depression. However, there are practical problems in recruiting sufficient numbers of patients with psychotic depression and therefore practitioners may wish to consider lower levels of evidence.

8.2.4.5 Recommendations for the pharmacological management of psychotic depression

8.2.4.5.1 For patients with psychotic depression consideration should be given to the augmentation of the current treatment plan with antipsychotic medication, although the optimum dose and duration of treatment are unknown. (C)

8.2.4.6 Research recommendations for the pharmacological management of psychotic depression

An adequately powered RCT reporting all relevant outcomes should be undertaken to assess the efficacy of antipsychotics in the treatment of psychotic depression.

8.2.5 The pharmacological management of atypical depression

8.2.5.1 Introduction

Depression with atypical features is described in DSM IV (APA, 1994). The introduction of a formally defined type of depression with atypical features was in response to research and clinical data indicating that patients with atypical features have specific characteristics. The classical atypical features are over-eating and over-sleeping (sometimes referred to as reverse vegetative symptoms). The syndrome is also associated with mood reactivity, leaden psychosis and a longstanding pattern of interpersonal rejection sensitivity. In comparison to major depressive disorder without atypical features, patients with atypical features are more often female, have a younger age of onset and a more severe degree of psychomotor slowing. Co-existing diagnoses of panic disorder, substance abuse and somatisation disorder are common. The high incidence and severity of anxiety symptoms in these patients increases the likelihood of their

being misclassified as having an anxiety disorder. The major treatment implication of atypical features is that patients are said to be more likely to respond to a monoamine oxidase inhibitor than to tricyclic drugs. However the significance of atypical features remains controversial as does the preferential treatment response to monoamine oxidase inhibitors. The absence of specific diagnostic criteria has limited the ability to assess the aetiology, prevalence and validity of the condition.

8.2.5.2 Studies considered for review

This section brings together studies from other reviews undertaken for this guideline where participants were diagnosed with atypical depression. A separate systematic search of the literature was not undertaken and, therefore, studies undertaken with atypical depression using drugs not reviewed for this guideline are not included.

In all three studies from other reviews were of typical depression (MCGRATH2000, PANDE1996, QUITKIN1990). Two came from the review of phenelzine and one from the review of SSRIs. Data were available to look at the efficacy phenelzine, SSRIs and TCAs, but the tolerability of only phenelzine. Data Phenelzine was compared with imipramine/desipramine or with fluoxetine; fluoxetine was compared with phenelzine or imipramine; and imipramine/ desipramine was compared with fluoxetine and phenelzine. Efficacy data were available from up to 334 patients, and tolerability data from up to 40 patients. All included studies were published between 1990 and 2000. Two were classified outpatient studies and in the other it was not possible to determine the source.

8.2.5.3 Evidence statements

Effect of treatment on efficacy

In people with atypical depression there some evidence suggesting that there is a clinically significant difference favouring phenelzine over alternative antidepressants on:

- achieving a 50% decrease in depression symptoms by the end of treatment as measured by the HRSD (N= 2; n= 232; RR= 0.69; 95% CI, 0.52 to 0.9)
- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N= 2;n= 232;RR=0.7; 95% CI, 0.53 to 0.93).

In people with atypical depression there is evidence suggesting that there is a statistically significant difference favouring phenelzine over alternative antidepressants on reducing depression symptoms as measured by the HRSD but there is insufficient evidence to determine its clinical significance (N= 2; n= 232; SMD = -0.39; 95% CI, -0.66 to -0.12).

In people with atypical depression there is insufficient evidence to determine if there is a clinically significant difference between fluoxetine and phenelzine on any efficacy measure.

Acceptability and tolerability of treatment

In people with atypical depression there is insufficient evidence to determine if there is a clinically significant difference between phenelzine and fluoxetine on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

8.2.5.4 Clinical summary

In patients with atypical depression there is some evidence suggesting a clinical advantage for phenelzine over other antidepressants in terms of achieving remission and response, but insufficient evidence that there is an advantage with respect to tolerability.

8.2.5.5 Recommendations for the pharmacological management of atypical depression

8.2.5.5.1 Patients whose depression has atypical features should be treated with an SSRI. (C)

8.2.5.5.2 All patients receiving phenelzine require careful monitoring and advice on interactions with other medicines and foodstuffs, and should have their attention drawn to the product information leaflet. (C)

8.2.5.5.3 Consideration should be given to referring those patients with atypical depression and significant functional impairment who have not responded to an SSRI to mental health specialists. (GPP)

8.2.5.6 Research recommendations

An adequately powered RCT reporting all relevant outcomes to determine the effectiveness of antidepressants in combination with antipsychotics in the treatment of psychotic unipolar depression should be undertaken.

8.2.6 The pharmacological management of relapse prevention

8.2.6.1 Introduction

Major depressive disorder is amongst the most important cause of death and disability worldwide in both developing and developed countries (Murray and Lopez, 1997). Because of the long-term nature of depressive disorder with many patients at substantial risk of later recurrence, there is a considerable need to establish how long such patients should stay on antidepressants. Existing clinical guidelines recommend that treatment should be continued for four to six months after the acute episode (Anderson et al, 2000, American Psychiatric Association, 2000, Bauer et al, 2002). There is a considerable variation in practice suggesting that many patients do not receive optimum treatment. Recently Geddes et al, (2003) reviewed all trials published and unpublished available for review by August 2000 in which continued antidepressant drug therapy was compared with placebo in patient who had responded to acute treatment with antidepressants. It was found that antidepressants reduced the risk of relapse in depressive disorder and continued treatment with antidepressants appeared to benefit many patients with recurrent depressive disorder. The treatment benefit for an individual patient depended on their absolute risk of relapse with greater absolute benefits in those at higher risk. It was estimated that for patients who were still at appreciable risk of recurrence after four to six months of treatment with antidepressants, another year of continuation treatment would approximately halve their risk. The authors found no evidence to support the contention that the risk of relapse after withdrawal from active treatment in the placebo group was due to a direct pharmacological effect (e.g., 'withdrawal' or 'rebound') since there was not an excess of cases within a month of drug discontinuation.

8.2.6.2 Studies considered for review

The GDG used the review by Geddes et al. (2003) as the basis for this section. The original review included 37 studies of which twenty met the inclusion criteria set by the GDG. An additional five studies were identified in new searches, one of which was excluded. Another study was identified through searching journal tables of contents and a further study was identified from searches undertaken for the review of lithium augmentation elsewhere in this guideline. Both of these were included. Therefore, 26 studies for the basis of this review (ALEXOPOULOUS2000, BAUER2000, COOK1986, DOOGAN1992, FEIGER1999, FRANK1990, GEORGOTAS1989, GILABERTE2001, HOCHSTRASSER2001, KELLER1998, KISHIMOTO1994, KLYSNER2002, KUPFER1992, MONTGOMERY1988, MONTGOMERY1992, MONTGOMERY1993, PRIEN1984, REIMHERR1998, ROBERT1995, ROBINSON1991, SACKHEIM2001,

SCHMIDT2000, TERRA1998, THASE2001, VERSIANI1999, WILSON2003) and eighteen excluded.

Studies included a pre-maintenance phase during which participants continued to receive medication after they had achieved remission. This was followed by a maintenance phase in which participants who had achieved remission were randomised either to pharmacological treatment or to placebo. Studies were included provided participants were classified as remitted only if they no longer met diagnosis for major depression or had achieved an HRSD or MADRS score below the cut-off for mild depression. Similarly, studies were included only if participants had been assessed as having relapsed using some kind of formal criteria such as exceeding a specific HRSD or MADRS score or meeting formal diagnostic criteria for depression rather than clinical judgement alone.

A single outcome, number of study participants experiencing relapse, was extracted. Since the length of both the pre-maintenance and the maintenance phase varied between studies, sub-analyses were undertaken splitting the dataset as follows:

- By length of continuation treatment (i.e., length of time continued with medication after remission but before randomisation) – less than or more than six months
- By length of maintenance treatment – less than or more than twelve months

The longest maintenance phase was two years. Further sub-analyses were undertaken combining these factors – for example, studies with pre-maintenance treatment of less than six months and maintenance treatment of less than twelve months.

Twelve studies used an SSRI as the maintenance treatment (2,342 participants), seven studies used a TCA (363 participants), and five studies used other antidepressants (651 participants). Three studies (BAUER2000, PRIEN1984, SACKHEIM2001) compared lithium (with and without an antidepressant) with an antidepressant or placebo. (One four-arm trial (PRIEN1984) has both antidepressant and lithium treatment groups.) Twenty-one studies used the same treatment in both acute and maintenance phases, and three did not.

All included studies were published between 1984 and 2003. In seventeen studies participants were described as outpatients, one was from primary care and in the other eight it was either not clear from where participants were sourced or they were from mixed sources. There were no studies of inpatients. Five studies were classified elderly, and none were of atypical depression.

Of the 24 trials of antidepressant medication, twelve (BAUER2000, COOK1986, FRANK1990, GILBARERTE2001, HOCHSTRASSER2001, KISHIMOTO1994,

KUPFER1992, MONTGOMERY1988, MONTGOMERY1993, ROBINSON1991, TERRA1998 VERSIANI1999) included only participants who had had at least one previous depressive episode. Five studies (ALEXOPOULOS2000, FEIGER1999, KLYSNER2002, THASE2001, WILSON2003) were of participants with a mix of first episode and previous episode depression. For the purpose of a sub-analysis by number of episodes, two of these (KLYSNER2002, WILSON2003) were classified first episode since more than 70% of participants were in their first episode. In the remaining seven studies (DOOGAN1991, GEORGOTAS1989, KELLER1998, MONTGOMERY1992, ROBERT1995, SCHMIDT2000, SACKHEIM2001) it was not possible to assess the proportion of participants with first or subsequent episode depression. Additional sub-analyses were undertaken by number of previous episodes.

8.2.6.3 Evidence statements

Effect of treatment on relapse

In an analysis of all available data comparing maintenance treatment with an antidepressant with placebo, there is strong evidence suggesting that there is a clinically significant difference favouring continuing antidepressant treatment over discontinuing antidepressant treatment on reducing the likelihood of relapse (N= 24; n= 3356; RR= 0.43; 95% CI, 0.39 to 0.48).

There was little difference in the results of sub-analyses by length of pre-randomisation treatment or by post-randomisation treatment, by a combination of these factors, or between results for SSRIs and TCAs analysed separately. Nor was any difference found for patients in their first episode or for those with previous episodes.

With regard to lithium augmentation:

There is some evidence suggesting that there is a clinically significant difference on reducing the likelihood of relapse favouring continuing lithium augmentation of an antidepressant over:

- discontinuing lithium (i.e., continuing on antidepressant monotherapy) (N= 3; n= 160; RR= 0.58; 95% CI, 0.37 to 0.92).

- discontinuing lithium and antidepressant treatment (i.e., taking a placebo) (N= 2; n= 129; RR= 0.42; 95% CI, 0.28 to 0.64).

In patients who have achieved remission whilst taking an antidepressant plus lithium, there is some evidence suggesting that there is a clinically significant difference favouring discontinuing lithium treatment (i.e., continuing with the

antidepressant alone) over discontinuing antidepressant treatment (i.e., continuing lithium alone) on reducing the likelihood of patients experiencing a relapse in depression symptoms (N= 1; n= 77; RR= 1.75; 95% CI, 1.03 to 2.96).

In patients who have achieved remission whilst taking an antidepressant plus lithium there is insufficient evidence to determine if there is a clinically significant difference between discontinuing antidepressant treatment (continuing with lithium alone) and discontinuing antidepressant and lithium treatment (taking a placebo) on reducing the likelihood of patients experiencing a relapse in depression symptoms (N=1; n=71; RR=0.88; 95% CI, 0.60 to 1.28).

Clinical summary

The majority of study participants had experienced multiple depressive episodes. There is strong evidence that responders to medication, who have had multiple relapses, should stay on medication to avoid relapse, irrespective of the length of treatment pre-response (between 6 weeks and 12 months). This effect holds true beyond 12 months. From the available data, it is not possible to determine effects beyond two years. These effects were evident with both TCAs and SSRIs. Whether this effect is evident in those recovering from a first episode or with placebo is unknown. Since most studies randomised participants either to continue with medication or to a placebo, there is little data comparing lengths of maintenance treatment with active medication.

It is worthwhile continuing treatment for up to two years. For patients who have achieved remission whilst taking lithium in addition to an antidepressant it appears to be worthwhile continuing treatment. If one or other drug is stopped the evidence suggests that lithium should be stopped in preference to the antidepressant.

8.2.6.4 Recommendations for relapse prevention

8.2.6.4.1 For patients with a depressive episode antidepressants should be continued for at least 6 months following remission because this greatly reduces the risk of relapse. (A)

8.2.6.4.2 For patients who have taken antidepressants for 6 months after remission healthcare practitioners should, in conjunction with the patient, review the need for continued antidepressant treatment. This review may include consideration of the number of previous episodes, presence of residual symptoms, and concurrent psychosocial difficulties. (GPP)

8.2.6.4.3 Patients who have had two or more depressive episodes in the recent past and who have experienced functional impairment during the episodes should be advised to continue antidepressants for 2 years. (B)

8.2.6.4.4 Patients on maintenance treatment should be re-evaluated taking into account age, comorbid conditions and other risk factors in the decision to continue maintenance treatment beyond 2 years. (GPP)

8.2.6.4.5 The antidepressant dose used for the prevention of recurrence should be maintained at the level at which acute treatment was effective. (C)

8.2.6.4.6 Patients who have had multiple episodes of depression, who are treated by mental health services, and who have had a good response to treatment with an antidepressant and lithium augmentation, should remain on this combination for at least 6 months. (B)

8.2.6.4.7 For patients who are treated by specialist mental health services on an antidepressant with lithium augmentation, if one or other drug is to be discontinued this should be lithium in preference to the antidepressant. (C)

8.2.6.4.8 The use of lithium as the sole agent to prevent recurrence in patients with previous recurrences is not recommended. (C)

8.2.6.5 Research recommendations

Adequately powered RCTs should be undertaken to ascertain the optimum lengths of both acute-phase and maintenance treatment as well as the optimum maintenance dose.

8.2.7 Dosage issues

8.2.7.1 Low dose versus high dose TCAs

There is controversy whether the existing recommended dosages for TCAs (100mg/day, Bollini et al, 1999) are too high with GPs being criticised for prescribing at doses which are too low whilst evidence for dosing levels are not established (Furukawa et al., 2002). This review compares the efficacy and tolerability of low and high doses of TCAs. Low doses were those where the mean dose achieved was less than the equivalent of 100mg of amitriptyline.

8.2.7.2 Studies considered for review

The GDG used an existing review (Furukawa et al., 2002) as the basis for this review. The original review included 38 studies of which 33 did not meet the

inclusion criteria set by the GDG, mainly because of inadequate diagnosis of depression. Therefore five trials (BURCH1988, DANISH1999, ROUILLON1994, SIMPSON1988, WHO1986) are included in this review providing data from up to 222 participants.

All included studies were published between 1988 and 1999 and were between four and eight weeks long (mean = six weeks). One study was of inpatients and two of outpatients, with none in primary care. Patients in one study were from mixed sources (DANISH1999). It was not possible to discern setting in WHO1986. No study included all elderly participants or those with atypical features. Study inclusion criteria ensured a minimum HRSD score at baseline of between 16 and 22 or a MADRS score of 15.

Data were available to compare low doses with high doses of clomipramine, amitriptyline, trimipramine and imipramine. Data were also available to compare low-dose clomipramine with placebo.

Mean low dose was 60.8mg (total range 25mg to 75mg) and mean high dose was 161.9mg (total range 75mg to 200mg) (low dose versus high dose studies).

8.2.7.3 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference between low dose TCAs and high dose TCAs on increasing the likelihood of achieving remission by the end of treatment (N= 3; n= 222; RR= 0.99; 95% CI, 0.84 to 1.16).

There is insufficient evidence to determine whether there is a clinically significant difference between low does TCAs and high dose TCAs on achieving a 50% reduction in depression symptoms or on reducing depression symptoms as measured by the HRSD.

There is insufficient evidence to determine whether there is a clinically significant difference between low dose TCAs and placebo on reducing depressions symptoms by the end of treatment as measured by the MADRS or on achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD.

Acceptability and tolerability of treatment

There is some evidence suggesting that there is a clinically significant difference between low dose TCAs over high dose TCAs, with fewer patients receiving low

dose TCAs leaving the study early due to side effects (N= 1; n= 151; RR= 0.35; 95% CI, 0.16 to 0.78).

There is insufficient evidence to determine whether there is a clinically significant difference between low dose TCAs and high dose TCAs on reducing the likelihood of patients leaving treatment early.

8.2.7.4 Clinical summary

There is no clinically significant difference on achieving response between low dose TCAs (mean dose = 60.8mg) and therapeutic dose TCAs (mean dose = 161.9mg). Of the four studies which compared low dose TCA with high dose TCA, two reported completer data only. Patients receiving a low dose TCA were less likely to leave treatment early due to side effects.

8.2.7.5 Recommendations

8.2.7.5.1 Patients who start on low dose tricyclic antidepressants and who have a clear clinical response can be maintained on that dose with careful monitoring. (C)

8.2.7.5.2 Patients started on low dose tricyclic antidepressants should be carefully monitored for side effects and efficacy and the dose gradually increased if there is lack of efficacy and no major side effects. (GPP)

8.2.8 Antidepressant discontinuation symptoms

8.2.8.1 Introduction

The term 'discontinuation syndrome' describes the range of symptoms that can be experienced on stopping prescribed drugs which are not drugs of dependence. Discontinuation symptoms can occur after stopping many drugs, including antidepressants and may be explained in the context of 'receptor rebound', for example, an antidepressant with potent anticholinergic side-effects may be associated with diarrhoea on withdrawal.

Discontinuation symptoms may be new or hard to distinguish from some of the original symptoms of the underlying illness. By definition they must not be attributable to other causes. They are experienced by at least a third of patients (Lejoyeux et al., 1996).

The onset is usually within five days of stopping treatment (depending on the half-life of the antidepressant) or occasionally during taper or after missed doses (Rosenbaum et al., 1998, Michelson et al., 2000) (short half-life drugs only). Symptoms can vary in form and intensity and occur in any combination. They are usually mild and self-limiting, but can occasionally be severe and prolonged.

Some symptoms are more likely with individual drugs (Lejoyeux et al., 1996, Haddad, 2001) (see Table 1).

Table 1

	MAOIs	**TCAs**	**SSRIs & venlafaxine**
	Common		
Symptoms	Agitation Irritability Ataxia Movement disorders insomnia Somnolence Vivid dreams Cognitive impairment Slowed speech Pressured speech	'Flu-like symptoms (chills, myalgia, excessive sweating, headache, nausea) Insomnia Excessive dreaming	'Flu-like symptoms 'shock-like' sensations Dizziness exacerbated by movement Insomnia Excessive dreaming Irritability Crying spells
	Occasional		
	Hallucinations Paranoid delusions	Movement disorders Mania Cardiac arrhythmias	Movement disorders Problems with concentration and memory

8.2.8.2 Who is most at risk?

Although anyone can experience discontinuation symptoms, the risk is increased in those prescribed short half-life drugs (Rosenbaum et al., 1998) (eg paroxetine (ibid., Hindmarsh et al., 2000), venlafaxine (Fava et al., 1997)). This can occur in patients who do not take their medication regularly. Two-thirds of patients prescribed antidepressants skip a few doses from time to time (Meijer et al., 2001). The risk is also increased in those who have been taking antidepressants for eight weeks or longer (Haddad, 2001), those who developed anxiety symptoms at the start of antidepressant therapy (particularly with SSRIs), those receiving other centrally acting medication (eg antihypertensives, antihistamines, antipsychotics), children and adolescents and those who have experienced discontinuation symptoms before (Lejoyeux & Ades, 1997, Haddad, 2001).

Discontinuation symptoms may also be more common in those who relapse on stopping antidepressants (Zajecka et al., 1998, Markowitz et al., 2000).

8.2.8.3 Clinical relevance

The symptoms of a discontinuation reaction may be mistaken for a relapse of illness or the emergence of a new physical illness (Haddad, 2001) leading to unnecessary investigations or reintroduction of the antidepressant. Symptoms may be severe enough to interfere with daily functioning. Another point of clinical relevance is that patients who experience discontinuation symptoms may assume that this means that antidepressants are addictive and not wish to accept further treatment. It is very important to counsel patients before, during and after antidepressant therapy about the nature of this syndrome.

8.2.8.4 How to avoid

Generally, antidepressant therapy should be discontinued over at least a 4 week period (this is not required with fluoxetine) (Rosenbaum et al., 1998). The shorter the half-life of the drug, the more important that this rule is followed. The end of the taper may need to be slower as symptoms may not appear until the reduction in the total daily dosage of the antidepressant is substantial. Patients receiving MAOIs may need to be tapered over a longer period. Tranylcypromine may be particularly difficult to stop. It is not clear if the need for slow discontinuation of MAOIs and particularly tranylcypromine is due to the discontinuation syndrome or the loss of other neurochemical effects of these drugs. Since it is not possible to disentangle these phenomena the clinical advice is that patients on MAOIs and those at risk patients (see above) need a slower taper (Haddad, 2001).

8.2.8.5 How to treat

There are no systematic randomised studies in this area. Treatment is pragmatic. If symptoms are mild, reassure the patient that these symptoms are not uncommon after discontinuing an antidepressant and will pass in a few days. If symptoms are severe, reintroduce the original antidepressant (or another with a longer half-life from the same class) and taper gradually while monitoring for symptoms (Lejoyeux & Ades, 1997, Haddad, 2001).

8.2.8.6 Recommendations regarding discontinuation symptoms

8.2.8.6.1 Patients started on antidepressants should be seen on a regular basis and carefully monitored for side effects and efficacy. (GPP)

8.2.8.6.2 All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects and of the

risk of discontinuation symptoms (particularly with paroxetine and venlafaxine).(C)

8.2.8.6.3 All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe. (C)

8.2.8.6.4 Patients should be advised to take the drugs regularly during a course. This is particularly important with short half-life drugs, such as paroxetine and venlafaxine. (C)

8.2.8.6.5 Healthcare professionals should normally gradually reduce the doses of the drug over a 4-week period, apart from fluoxetine, which can usually be stopped abruptly. (C)

8.2.8.6.6 If discontinuation symptoms are mild, practitioners should reassure the patient and arrange for monitoring. If severe symptoms are experienced consider the reintroduction of the original antidepressant (or another with a longer half-life from the same class) and reduce gradually while monitoring symptoms. (C)

8.2.8.6.7 Healthcare professionals should inform patients that if they experience significant discontinuation symptoms they should seek advice from their medical practitioner. (GPP)

8.2.9 The cardiotoxicity of antidepressants

Consistent associations between depression and cardiovascular morbidity and mortality have been identified (Glassman and Shapiro, 1998). Depression is a significant independent risk factor for both first myocardial infarction and cardiovascular mortality with an adjusted relative risk in the range of 1.5 – 2 (for et al 1998). In patients with ischaemic heart disease, depression has been found to be associated with a three to four fold increase in cardiovascular morbidity and mortality (Carney et al., 1997). The prevalence of major depression in patients with coronary heart disease is approximately twenty per cent (Glassman et al 2002).

In view of the above associations and factors it is important to use antidepressant drugs that either reduce or do not increase the cardiovascular risk of the condition itself and to establish a safe and effective treatment strategy for depressed patients with heart disease. There is evidence that adequate treatment of depression appears to either lower (Avery and Winokur, 1976) or not to

change (Pratt et al, 1996) the risk of heart disease. However, two large-scale follow-up studies have shown an increase in myocardial infarction in users of antidepressants with an average odds ratio of 5.8 (Penttinen et al., 1986, Thorogood et al., 1992). Recently a similar association has been identified in the United Kingdom for dosulepin (Hippersley-Cox et al., 2002).

However these studies do not distinguish between the effects of drugs and the condition itself. Thus it is necessary to look at the effects of antidepressants on cardiovascular function and what trials are available.

8.2.9.1 Tricyclic antidepressants

Sinus tachycardia, postural hypotension and episodic hypertension are side effects frequently observed. ECG changes are frequent such a lengthening of the QT, PR and QRS intervals relating to alterations in AV conduction and repolarisation (Roose et al., 2003). These effects are due to the wide ranging pharmacological actions of TCAs that are not correlated with recognised mechanisms of antidepressant action. In healthy patients such changes may be asymptomatic or clinically unimportant, but in those with heart disease they may lead to significant morbidity and mortality (Glassman et al 1993). For example prolonged increased heart rate (mean 11%, Roose & Glassman, 1989) could have a major impact in terms of cardiac work (Roose, 2003). In patients with left ventricular impairment on TCAs, orthostatic hypotension is three to seven times more common and potentially clinically harmful (Glassman et al., 1983). The TCA induced prolongation of conduction may be clinically unimportant in healthy patients, but can lead to complications in those with conduction disease, in particular bundle branch block, and these can be severe in twenty per cent of subjects (Roose et al., 1987). TCAs may be regarded as class I arrhythmic drugs. Evidence suggests that this class of drug is associated with an increase in mortality in post infarction patients and in patients with a broader range of ischemic disease probably because they turn out to be arrhythmogenic when cardiac tissue becomes anoxic. Overdose of TCAs or elevated plasma levels as a result of interactions with other drugs, liver disease and age is associated with serious hypotension and atrial and ventricular arrthymias may arise even to the extent of complete AV block which in a number of cases may be fatal (deaths from TCAs represent 20% of overdose deaths, Shah et al., 2001).

Individual Tricyclics

The tertiary amine tricyclics (amitriptyline, imipramine and clomipramine) have more cardiovascular effects than the secondary amine tricyclics (e.g., nortriptyline). The latter drug has been shown to have less postural hypotension and therefore may be considered in those with cardiovascular disease and in the elderly in whom postural hypotension can be very hazardous. There is evidence (although not from an RCT) that lofepramine is safer in overdose than other tricyclics (Lancaster & Gonzalez, 1989). It is thought that lofepramine blocks the

cardio toxic effects of the main metabolite desipramine. Dosulepin has marked toxicity in overdose in uncontrolled studies (Henry et al., 1992, Buckley et al., 1994).

8.2.9.2 Selective serotonin reuptake inhibitors

Depression in untreated populations has been demonstrated to increase cardiovascular morbidity and mortality. SSRIs appear to reduce that risk, since two studies have reported no difference in cardiovascular risk between SSRI's treated depressed patients and non-treated non-depressed controls (Cohen et al., 2000, Meier et al., 2001). Recently (Sauer et al., 2001) compared the rate of MI in patients on an SSRI with those on no antidepressants. The SSRI-treated patients had a significantly lower rate of MI than did the non SSRI-treated patients. Multiple studies (Roose, 2001) reveal no clinically significant effects of SSRIs on heart rate, cardiac conduction or blood pressure (see further details below). Studies of depressed patients with and without ischemic heart disease have documented increased platelet activation and aggregation which potentially contributes to thrombus formation (Musselman et al., 1998). Treatment with SSRIs normalises elevated indices of platelet activation and aggregation seen in non-treated patients with depression and IHD. There is evidence that this effect occurs at relatively low doses and before the antidepressant effect (Pollock et al., 2000). However, the effects on platelet serotonin is not always advantageous: SSRIs increase the probability of having a serious GI bleed, particularly in the very old (Walraven et al., 2001).

8.2.9.3 Individual drugs

Citalopram

The cardiac safety of citalopram has been studied in prospective studies in volunteers and patients and in retrospective evaluations of all ECG data from forty clinical trials (1,789 citalopram-treated patients) (Rasmussen et al., 1999). The only effect of citalopram was the reduction in heart rate (of eight beats per minute) but no other ECG change. There have been case reports of bradycardia with citalopram (Isbister et al., 2001) and a low frequency of hypotension and arrythmias including left bundle branch block (Mucci, 1997).

Fluoxetine

Roose et al. (1998) showed that fluoxetine caused no major cardiovascular change in a seven-week open trial of elderly patients with cardiac disease. Strik et al. (2000) showed that fluoxetine was safe in 27 patients with recent MI (more than three months since the MI) and there was no change in cardiovascular indices in these patients compared with placebo. However, fluoxetine did not demonstrate clinical efficacy in this group compared with placebo (n=54; WMD= -2.50, 95%

CIs –5.64 to 0.64). It is noteworthy that fluoxetine has significant potential to interact with drugs commonly used in the management of heart disease (Mitchell, 1997).

Fluvoxamine

Fluvoxamine has not been found to be associated with cardiovascular or ECG changes (Hewer et al, 1995). Fluvoxamine appears to be safe in overdose (Garnier et al, 1993). Cardiotoxicity was not a serious problem: sinus bradycardia requiring no treatment was noted in a few cases.

Paroxetine

20mg – 30 mg paroxetine daily was compared to nortriptyline (dose adjusted to give plasma concentrations of 80 to 120 ng/ml) in a double blind study of forty one patients with MDD and IHD (Roose et al 1997). Paroxetine was not associated with clinically significantly sustained changes in heart rate, blood pressure or conduction intervals whereas nortriptyline caused 'clinically significant' changes in these measures and 'more serious cardiac events'.

Sertraline

Three hundred and sixty-nine patients with either unstable angina (26%) or recent (within thirty days) MI (74%) were randomised to receive either placebo or sertraline (flexible dose, 50 mg to 200 mg per day in a randomised double blind trial) (Glassman et al 2002). Sertraline had no significant effect on left ventricular function compared to placebo or on a range of clinical or laboratory investigations. The incidence of severe cardiovascular events was 14.5 per cent with sertraline numerically, but not significantly, less than placebo at 22.4 per cent.

There was no overall difference between sertraline and placebo in terms of antidepressant response in all patients studied. However, in more severely depressed patients (HRSD >=18 and at least two previous depressive episodes), there was some evidence of a greater decrease in depression symptoms in those on SSRIs compared with those on placebo (n=90; WMD= -3.4, 95% CIs, -6.47 to -0.33[41]). However, this study and others in the field are not adequately powered or of sufficient length to determine cardiovascular morbidity in mortality in the longer term.

Overdose

In contrast to the TCA the SSRIs, if taken alone, are only rarely lethal in overdose (Barbey et al., 1998, Goeringer et al., 2000). Deaths have occurred when citalopram has been ingested in very high doses (Ostrom et al., 1996). Although

[41] These data were calculated from data in the paper.

other studies, whilst reporting complications with high-dose citalopram overdoses have not reported deaths (Personne et al., 1997; Grundemar et al., 1997). The mechanisms of the deaths reported by Ostrom et al. (1996) is not clear. There is some evidence that high doses citalopram overdoses have been associated with ECG abnormalities (Personne et al., 1997) and QTc prolongation (Catalono et al., 2001). However, Boeck et al. (1982) did not report cardiotoxicity with high dose citalopram in the dog and in the deaths reported by Ostrom et al. (1996) levels of the potentially cardiotoxic metabolite were low. Another potential mechanism of toxicity is that high-dose citalopram overdoses induce seizures and this has been shown in animals (Boeck et al., 1982) and man (Grundemar et al., 1997; Personne et al., 1997). Glassman (1997) suggested that all high-dose SSRI overdoses were a cause for concern and advised prudence over the prescription of large amounts of tablets.

Other Drugs

Lithium

Lithium has a number of cardiac effects and they can be of clinical significance in those with heart disease, the elderly, those with higher lithium levels, hypokalaemia and when lithium is used with other drugs such as diuretics, hydroxyzine and tricyclic antidepressants (Chong et al., 2001). Common, often subclinical, effects of lithium include the "sick sinus" syndrome, first degree heart block, ventricular ectopics, flattened T-waves and increased QT dispersion (Reilly et al., 2000) but adverse clinical outcomes are rare. Caution and periodic ECG monitoring is advised in those at risk or with cardiac symptoms.

Mianserin

Cardiac effects with mianserin are rare (Peet et al., 1977, Edwards & Goldie., 1983, Jackson et al., 1987) although there have been some reports of bradycardia and complete heart block in overdose (Haefeli et al., 1991, Hla & Boyd., 1987) and rarely, bradycardia at therapeutic doses (Carcone et al., 1991). Bucknall et al. (1998) showed that mianserin was well tolerated in most, but not all, cardiac patients.

Mirtazapine

No significant cardiovascular effects from Mirtazapine have been noted (Nutt, 2002). It appears to have a benign safety profile in overdose (Velasquez et al., 2001).

Moclobemide

Moclobemide is not associated with any significant cardiovascular effects (Fulton & Benfield, 1996) and there are no reports of death in overdose with moclobemide as the sole agent.

Phenelzine

Phenelzine causes marked postural hypotension particularly in the early weeks of treatment and it is associated with a significant bradycardia. It does not cause conduction defects (McGrath et al., 1997). Its fatal toxicity index in overdose appears to be less than most tricyclics (Henry et al., 1992). There is no data on the safety or clinical efficacy of phenelzine in patients with ischemic heart disease.

Reboxetine

No specific clinical or ECG abnormalities have been noted with reboxetine (Fleishaker et al., 2001) and it has relative safety in overdose.

Trazodone

Trazodone is generally believed to have low cardiotoxicity, although these have been some reports of postural hypotension and, rarely, arrthymias (Janowsky et al., 1983).

Venlafaxine

No obvious laboratory or clinical cardiac changes have been found with venlafaxine in routine use (Feighner, 1995). There is evidence that in higher doses greater than 200 mg hypertension occurs in a small but significant minority and regular blood pressure monitoring is recommended at and above this dose (Feighner, 1995). There is evidence that in overdose (greater than 900 mg) Venlafaxine in pro convulsant compared to TCAs and SSRIs (Whyte et al., 2003) and has a higher fatal toxicity index in overdose than SSRIs (Buckley & McManners, 2002). There are no data examining venlafaxine in patients with ischemic heart disease.

8.2.9.4 Recommendations regarding antidepressant cardiotoxicity

8.2.9.4.1 When initiating treatment in a patient with a recent myocardial infarction or unstable angina, sertraline is the treatment of choice. (B)

8.2.9.4.2 Healthcare professionals should take account of the increased risks associated with tricyclic antidepressants in patients with cardiovascular disease. (GPP)

8.2.9.4.3 When considering prescribing tricyclic antidepressants for a depressed patient at significant risk of cardiovascular disease, ECGs should be carried out. (GPP)

8.2.10 Depression, antidepressants and suicide

8.2.10.1 Introduction

The majority of patients with clinical depression have at least episodic suicidal ideation often linked to general negativity and hopelessness. Two thirds of attempted suicides are suffering from a depressive illness at the time of the suicide bid. Suicide is the main cause of the increased mortality of depression and is commonest in those with comorbid physical and mental illness. Suicidal behaviour also occurs with milder forms of depression. Harris and Barraclough (1997) found a suicide risk of twelve times that expected in a cohort of patients with dysthymia (DSM 111, which includes ICD 10 mild depression and ICD 9 neurotic depression). Antidepressants are not effective for the treatment of patients with suicidal ideation in the absence of a depressive disorder . The effective recognition and treatment of depression should lead to a fall in the overall suicide rate.

8.2.10.2 Suicidality and antidepressants

While a significant proportion of depressed suicide victims have received treatment for their depression very few have received an adequate dose or course of medication or psychotherapy. Suicidal ideation, intent and behaviour steadily improves over time with effective recognition and treatment of any underlying linked depression. Some authorities have argued that the significant reduction in suicide rate in Sweden, Hungary, the USA and Australia has been brought about at least in part by the more effective treatment of depression with the newer antidepressants (Isaacson et al., 1997, Hall et al., 2003). SSRIs have been postulated as one cause of falling suicide rates due to more effective treatment of the underlying depression due to improved tolerability and low toxicity in overdose. However, there is no evidence that antidepressants, including SSRIs, improve clinical outcomes of patients who have sub-threshold depression.

However, antidepressants are toxic in overdose and the older antidepressants, particularly the tricyclics are a common cause of fatal overdose. Tricyclics were the direct cause of death in 4.5% of suicide deaths in 1991 (Lewis, 1997) due to their cardiotoxic effects in overdose (see section on cardiotoxicity). Despite the overall beneficial effects on suicidality, there is uncertainty whether SSRIs are associated with increased suidicality (Kahn et al., 2003). There are two instances when suicidal behaviour can initially increase. The first of these is in more severe forms of depressive illness just after the initiation of hospital treatment when mood remains low with prominent guilt and hopelessness and when energy and motivation have increased. The second situation is with those outpatients who develop akathisia or increased anxiety due to a direct effect of an SSRI. The

reason for this phenomenon is not yet fully understood but may reflect 5HT2 sensitisation due to an increase in synaptic 5HT. In some patients this may increase the propensity to suicidal ideation and suicidal behaviour (Healey, 2003). Careful monitoring is therefore indicated when treatment is initiated with an SSRI or with venlafaxine which acts as an SSRI at low dose. Patients need therefore to be closely monitored even when their depression is mild in degree.

8.2.10.3 Recommendations

8.2.10.3.1 Healthcare professionals should not prescribe antidepressants for the treatment of patients with suicidal ideation in the absence of a depressive disorder. (C)

8.2.10.3.2 For patients who remain at high risk of suicide, consideration should be given to the appropriate quantity of antidepressant prescribed and the provision of additional support in the administration of medication. (GPP)

8.2.10.3.3 Toxicity in overdose should be considered when choosing an antidepressant for patients at significant risk of suicide. Healthcare professionals should be aware that SSRIs, lofepramine, mirtazapine and reboxetine are safer in overdose than other tricyclics or venlafaxine. (GPP)

8.2.10.3.4 Healthcare professionals should monitor for signs of akathisia and increased anxiety, which can lead to increased dysphoria and occasionally suicidal ideation in the early stages of treatment with an SSRI. (GPP)

8.2.10.4 Research recommendations

Suicidal ideation, self harming behaviour and completed suicide should be carefully and prospectively measured in large independent multi-centre trials using a variety of methodologies. Particular attention should be paid to the first four weeks of treatment.

Trials of antidepressants in other disorders e.g. chronic pain should similarly monitor for the above negative outcomes.

8.3 The pharmacological treatment of refractory depression

8.3.1 Introduction

Despite major developments in the management of mood disorders, in clinical practice the problem of treatment resistance continues to be problematic. Numerous outcome studies have demonstrated that approximately one-third of patients treated for major depression do not respond satisfactorily to first-round antidepressant pharmacotherapy. Follow up observations reveal that a considerable number of patients have a poor prognosis with as many as 20% remaining unwell two years after the onset of illness (Keller, 1986). Even after multiple treatments up to 10% of patients remains depressed (Nirenberg & Amsterdam, 1990). A range of studies suggests that between 10% and 20% of patients with major depressive disorder have a long-term poor outcome (Winokur et al., 1993, Lee et al., 1988).

It is difficult however to evaluate the true levels of resistance to treatment for major depressive disorder from these figures. Although treatment resistance is relatively common in clinical practice a major problem has been the inconsistent way in which it has been characterised and defined, limiting systematic research. The poor level of attention previously paid to any conceptual examination of treatment resistance has resulted in unsystematic research and uncontrolled trials which have led to a degree of confusion. However, more recently definitions have been agreed which have helped characterise the syndrome better although there is still disagreement on some of the items. The key parameters that characterise and define treatment resistance include the basic criteria used to specify the diagnosis, response to treatment, previous treatment trials and the adequacy of treatment (Nirenberg & Amsterdam, 1990).

For the purposes of assessing pharmacological treatments the GDG defined people with refractory depression as those whose depression symptoms had failed to respond to two or more antidepressants at an adequate dose for an adequate duration given sequentially. However, both trials where participants have failed one course of antidepressants and those where participants have failed more than one course are considered as part of the evidence base for this section. The terms 'acute-phase non-responders' and 'people with treatment resistant depression' are used to make it clear what kind of trial the evidence is from.

This chapter reviews the following treatment strategies:

- Switching strategies
- Venlafaxine for treatment resistant depression

- Augmentation strategies:
    - Augmenting an antidepressant with lithium
    - Augmenting an antidepressant with anticonvulsants (lamotrigine, carbamazepine or valproate)
    - Augmenting an antidepressant with another antidepressant
    - Augmenting an antidepressant with pindolol
    - Augmenting an antidepressant with triodothronine (T3)
    - Augmenting an antidepressant with a benzodiazepine
    - Augmenting an antidepressant with an antipsychotic
    - Augmenting an antidepressant with buspirone

The above strategies were reviewed as there was sufficient evidence to come to a conclusion about efficacy and/or significant clinical usage of such strategies in the UK. There are, however, a wide range of other strategies which are used in treatment resistance for which either the evidence base is so weak or the clinical usage so low that the CDG did not include them in this review. Examples of these latter strategies includes the use of MAOIs in combination with other drugs such as tricyclics or L-tryptophan and combinations of antidepressants for example SSRIs and tricyclics, venlafaxine and reboxetine or combinations of venlafaxine, mirtazepine and reboxetine. Details of the available information about these strategies (e.g. case reports, open studies, expert opinion) can be found elsewhere (Bauer et al., 2002, Price et al., 2001, Thase & Rush, 1997). These papers also include details of the pharmacological issues associated with these strategies. A wide variety of new treatments to augment antidepressants are being developed or are in pilot trial phase. These are beyond the scope of this review and details can be found elsewhere (Tamminga et al., 2002).

MAOIs have been used extensively in the management of TRD for four decades but there is no randomised data on which to base recommendations. Most information and experience is with phenelzine. McGrath et al. (1987) treated patients in a cross-over design with high doses of phenelzine (maximum 90 mg.) imipramine (maximum 300 mg.) or placebo and found that of the non-responders only four of the fourteen patients responded to a tricyclic cross-over with seventeen of the 26 patients responded to an MAOI cross-over. There was some evidence of a preferential response in treatment resistant patients with atypical depression symptoms but Nolen et al (1988) subsequently showed that not only patients with atypical depressive symptoms but also patients with major depression and melancholia responded to MAOIs in particular tranylcypramine. It does not appear that moclobemide has the same spectrum of efficacy in treatment resistance as the classical MAOIs. Nolen et al. (1994) switched patients with resistant depression stabilised on tranylcypromine to

moclobemide. About 60% of the patients showed deterioration and one third relapsed.

8.3.2 Switching strategies

8.3.2.1 Introduction

Approximately 20% to 30% of patients with depression fail to respond to the first antidepressant prescribed (assuming an adequate dose, duration of treatment and compliance with medication; Cowen, 1998). It is normal clinical practice at this point to increase the dose to the maximum tolerated (within licensed limits)and, if there is still no or minimal response, to switch to an alternative antidepressant (Anderson et al, 2000). Most prescribers select an antidepressant from a different class to the 'failed' drug (Fredman et al., 2000). Randomised studies of switching are difficult to interpret as they either include patients who may be expected to fare poorly on one of the treatments (e.g., patients with atypical depression in a study with a MAOI and TCA arm: McGrath et al., 1993) or employ a crossover design (Thase et al., 1992; McGrath et al.,1993). Open studies however show that approximately 50% of first treatment failure patients are likely to respond to the second antidepressant irrespective of whether it comes from the same class or a different one (Thase & Rush, 1997).

8.3.2.2 Studies considered for review

One study met the inclusion criteria set by the GDG (THASE2002). In this study participants were randomised to twelve weeks of treatment with either sertraline or imipramine. Non-responders were then switched to the other drug for a further twelve weeks. The mean dose of sertraline was 163 mg (+-48 mg) and that of imipramine 221 mg (+-84 mg).

8.3.2.3 Evidence statements

Effect of treatment on efficacy

There is insufficient evidence to determine if there is a clinically significant difference between switching from sertraline to imipramine and switching from imipramine to sertraline on achieving a 50% reduction in depression symptoms or on reducing depression symptoms.

Acceptability of treatment

There some evidence suggesting that there is a clinically significant difference favouring switching from imipramine to sertraline over switching from sertraline to imipramine on reducing the likelihood of leaving treatment early (N= 1; n= 168; RR= 2.53; 95% CI, 1.04 to 6.16).

8.3.2.4 Clinical summary

There is little evidence on which to make an evidence-based recommendation of switching strategies in the treatment of refractory depression.

8.3.3 Venlafaxine for treatment resistant depression

8.3.3.1 Introduction

At the standard dose of 75 mg, venlafaxine is a SSRI. At doses of 150 mg/day and above it also inhibits the reuptake of noradrenaline and to a lesser extent, dopamine. This progression from single to double to triple action is thought to be potentially beneficial in patients with treatment resistant depression. Venlafaxine is widely believed to be more effective than SSRIs in patients with treatment resistant depression.

8.3.3.2 Studies considered for review

In the section of venlafaxine elsewhere in this guideline only one study (POIRIER1999) included all treatment resistant patients. Here compared venlafaxine IR (mean dose 269 mg (plus-46.7)) is compared with paroxetine (20 mg up to 40 mg). Patients are either inpatients or outpatients aged between 21 and 62. The study was four weeks long.

8.3.3.3 Evidence statements

Effect of treatment on efficacy

In treatment resistant patients there some evidence suggesting that there is a clinically significant difference favouring venlafaxine over paroxetine on increasing the likelihood of achieving remission (N= 1; n= 123; RR= 0.78; 95% CI, 0.62 to 0.97).

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine and paroxetine on achieving a 50% reduction in depression symptoms or on reducing depression symptoms.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine and paroxetine on any measure of acceptability.

8.3.3.4 Clinical summary

In patients with treatment resistant depression, there is some evidence suggesting a clinical advantage for high dose venlafaxine (mean 269 mg) over paroxetine in terms of achieving remission, but insufficient evidence that this effect is evident with respect to response, mean endpoint scores or tolerability.

8.3.4 Augmentation strategies

8.3.4.1 Augmenting an antidepressant with lithium

Introduction

Lithium is an established mood stabilising drug that is used in the treatment of mania and the prophylaxis of bipolar affective disorder. It is also widely used to augment antidepressant response in treatment resistant unipolar depression. The mechanism of action of lithium is not clearly understood (Peet & Pratt, 1993).

Lithium is primarily renally excreted and can cause hypothyroidism. Baseline biochemical tests and ongoing monitoring is essential (full details can be found in the Maudsley Prescribing Guidelines, 2003).

Lithium is a potentially toxic drug. Plasma levels of 0.5-1.0mmol/L are usually considered to be therapeutic. Above 1.5mmol/L toxicity invariably develops and death may occur at levels as low as 2.0mmol/L. Many commonly prescribed drugs can interact with lithium to precipitate lithium toxicity (BNF, Maudsley Prescribing Guidelines, 2003).

Studies considered for review

Twenty-eight studies were found in a search of electronic databases, ten of which were included (BAUMANN1996, BLOCH1997, CAPPIELLO1998, JANUEL2002, JENSEN1992, JOFFE1993A, NIER'BERG03, SHAHAL1996, STEIN1993, ZUSKY1988) and 18 excluded in the present review.

Only studies comparing lithium plus an antidepressant with lithium plus placebo were included in the analyses. In place of the usual inclusion criterion relating to mean dose of study drugs, the GDG included trials only if they achieved a mean blood plasma level of 0.5 mmol/lL of lithium. Antidepressants used included clomipramine, desipramine, imipramine, nortriptyline and citalopram. One study used a variety of antidepressants but did not specify them (ZUSKY1988) and two studies used a range of unspecified TCAs (JOFFE1993A, STEIN1993).

All included studies were published between 1988 and 2002 with participants being randomised to an experimental treatment phase of between one and six weeks (mean = 4.2 weeks). BAUMANN1996, JOFFE1993A, STEIN1993, and ZUSKY1988 were classified as acute-phase non-responder trials. In BAUMANN1996 and JOFFE1993A participants were randomised to treatment only if they had not responded to between three and six weeks of open-label lithium augmentation. In STEIN1993 and ZUSKY1988 failure to respond to at least one course of antidepressant mono-therapy formed part of the trial inclusion criteria. (In addition 62% of those in CAPPIELLO1998 had failed one

course of antidepressants.) NIER'BERG03 was classified as a treatment-resistant trial since participants were included only if they had already failed between one and five courses of antidepressants and were randomised to treatment only if they failed to respond to an open-label course. The dataset was analysed three ways: all available studies, acute-phase non-responder trials and treatment resistant trials.

In four studies participants were described as inpatients (BAUMANN1996, JANUEL2002, JENSEN1992, SHAHAL1996), in three as outpatients (BLOCH1997, JOFFE1993A, NIER'BERG03), and in the other three it was either not clear from where participants were sourced or they were from mixed sources (CAPPIELLO1998, STEIN1993, ZUSKY1988). No trial was undertaken in primary care. In one (JENSEN1992) all participants were elderly.

Efficacy data were available from up to 237 participants and tolerability data from up to 356 participants. One hundred and forty-six participants were classified acute-phase non-responders and 35 treatment resistant.

Evidence statements for the complete data set

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring antidepressants augmented with lithium over antidepressants augmented with placebo on achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N= 6; n= 173; RR= 0.82; 95% CI, 0.68 to 0.99).

There is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on increasing the likelihood of achieving remission by the end of treatment (N= 3; n= 216; Random effects RR= 1.26; 95% CI, 0.73 to 2.17).

There is evidence suggesting that there is a statistically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on reducing depressions symptoms by the end of treatment as measured by the HRSD and the MADRS, but there is insufficient evidence to determine its clinical significance (N= 7; n= 273; SMD= -0.32; 95% CI, -0.56 to -0.08).

Acceptability of treatment

There is strong evidence suggesting that there is a clinically significant difference favouring antidepressants augmented with placebo over antidepressants

augmented with lithium on reducing the likelihood of leaving treatment early (N= 7; n= 356; RR= 1.79; 95% CI, 1.23 to 2.6).

There is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on either reducing the likelihood of leaving treatment early due to side-effects or reducing the likelihood of reporting side effects.

Evidence statements for acute-phase non-responder trials

Effect of treatment on efficacy outcomes

In patients who have failed one course of antidepressants, there is some evidence suggesting that there is a clinically significant difference favouring lithium over placebo on:

- achieving a 50% reduction in depression symptoms by the end of treatment as measured by HRSD (N= 3; n= 76; RR= 0.66; 95% CI, 0.49 to 0.9)
- reducing depression symptoms by the end of treatment as measured by the HRSD and MADRS (N= 4; n= 107; SMD= -0.48; 95% CI, -0.86 to -0.09).

Acceptability of treatment

In patients who have failed one course of antidepressants, there is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on reducing the likelihood of leaving treatment early (N= 1; n= 52; RR= 1.67; 95% CI, 0.56 to 4.97).

Evidence statements for treatment-resistant patients

Effect of treatment on efficacy outcomes

In treatment-resistant patients there is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on achieving a 50% reduction in depression symptoms by the end of treatment as measured by HRSD (N= 1; n= 35; RR= 1.08; 95% CI, 0.82 to 1.42).

Acceptability of treatment

In treatment-resistant patients there is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on reducing the likelihood of leaving treatment early in treatment-resistant patients (N= 1; n= 35; RR= 0.94; 95% CI, 0.15 to 5.97).

Clinical summary

In a mixed population of patients (45% acute-phase non-responders, 15% treatment resistant, 40% other depressed patients) there is some evidence of a clinically significant advantage of adding lithium to an antidepressant over adding placebo in terms of response rate though this effect was not found for mean endpoint scores. In acute-phase non-responders there is some evidence suggesting a clinical advantage of adding lithium over adding placebo in terms of response and mean endpoint scores. However there is insufficient evidence that this effect is evident in treatment resistant patients.

However, adding lithium to an antidepressant appears to be less acceptable to patients, although there is insufficient evidence to determine whether this is due to side effects.

8.3.4.2 Augmenting an antidepressant with anticonvulsants

Introduction

Anticonvulsants are increasingly being prescribed in bipolar disorder. There is a growing database on their efficacy in the treatment of depression and mania in bipolar disorder and in the prophylaxis of that condition. These developments, together with research, suggests that anticonvulsants may also help the symptoms of depression in the context of epilepsy, which have led to some trials and quite widespread use of anticonvulsants in unipolar disorder.

Carbamazepine

Carbamazepine has attracted the most interest since it was the first anticonvulsant to be shown to have efficacy in bipolar disorder and because carbamazepine shares some neurochemical properties with tricyclic antidepressants. However no RCTs met the inclusion criteria set by the GDG. There are some open studies in major depression (Dietrich and Emrich, 1998) and some in treatment resistant depression (Ketter et al, 1995, Cullen et al, 1991) which show some benefit. It is noteworthy that in Cullen's study a high percentage of the older patients who responded had to discontinue CBZ because of adverse effects.

Carbamazepine has a wide range of side effects, contraindications and interactions with other drugs. In the context of depression, it is noteworthy that carbamazepine co-administration reduces TCA levels by up to 50% (Dietrich and Emrich, 1998) and SSRIs may interfere with carbamazepine metabolism leading to intoxication.

There is a lack of controlled data and a high likelihood of adverse effects or clinically important interactions and therefore carbamazepine cannot be recommended in the routine management of treatment resistant depression.

Valproate

There are no RCTs of valproate in either major or bipolar depression. Evidence to date suggests that valproate is more effective in preventing hypomanias rather than depressions in bipolar disorder. One open study enrolled 33 patients with MDD in an eight-week study of valproate as monotherapy (Davis et al, 1996). Approximately 50% of the patients achieved remission. Valproate is generally well tolerated and there are few interactions with antidepressant drugs although fluoxetine may elevate valproate levels by interfering with its metabolism.

There is insufficient data on which to make an evidence-based recommendation for valproate in the treatment of depression. However, it could be used in a case where an anticonvulsant was required for other reasons.

Lamotrigine

Lamotrigine is an antiepileptic drug that is used in the treatment of partial and generalised seizures. In clinical trials in epilepsy a positive psychotropic effect was observed and mood, alertness and social interaction improved. Trials have shown that lamotrigine has evidence of efficacy in depression in bipolar disorder and in preventing depressive episodes particularly in bipolar II patients (Hurley, 2002). Hurley reports on an initial study of 437 MDD patients randomised to lamotrigine, desipramine or placebo. On 'last observation carried forward', ratings in these three groups were not significantly different from each other. In another study forty depressed patients (30 unipolar, 10 bipolar) were studied in a nine-week RCT of lamotrigine (200 mg) added to paroxetine (40 mg) against placebo. There was no difference in HRSD scores at end point compared with placebo alone (Normann et al, 2002). There was a high frequency of adverse effects and drop outs in both groups. Recently, Barbosa et al (2003) reported on a study of 23 depressed patients (65% MDD) who had failed at least one trial of an antidepressant. Patients were placed on fluoxetine 20 mg/day and then randomised to either placebo or 25 mg to 100 mg of lamotrigine. There was no statistical difference in HAMD or MADRA ratings between the two groups at six weeks.

In view of the lack of positive data lamotrigine cannot be recommended for use in unipolar disorder. Although it is generally well tolerated and free of major interactions, it can cause a severe rash which can be life threatening in a small minority of cases. Its profile in epilepsy and bipolar disorder suggests that further trials of lamotrigine in treatment resistant depression are worthwhile.

There are no data which indicate that other anticonvulsants – for example, gabapentin or topiramate - can be recommended in depression.

8.3.4.3 Augmenting an antidepressant with another antidepressant

Introduction

Combining antidepressant drugs with different modes of action is increasingly used in clinical practice. Combinations of serotonergic and noradrenergic drugs may result in a 'dual action' combination while combinations of serotonergic drugs with different modes of action may be expected to increase serotonergic neurotransmission more than either drug alone.

While the efficacy of these combinations may be additive (this is not proven for the majority of combinations), so too may the toxicity. Both pharmacokinetic and pharmacodynamic interactions must be considered. Fluoxetine, fluvoxamine and paroxetine may substantially and unpredictably increase TCA serum levels increasing the risk of adverse effects (Taylor, 1995). Combinations of serotonergic antidepressants increase the risk of developing serotonin syndrome which can be fatal.

Studies considered for review

Fifteen trials were found in a search of electronic databases, seven of which met the inclusion criteria set by the GDG (CARPENTER2002, FAVA1994, FAVA2002, FERRERI2001, LICHT2002, MAES1999, TANGHE1997). One study (TANGHE1997) included only treatment resistant patients and in another 65% were treatment resistant (MAES1999). Participants in the remaining studies were acute-phase non-responders. Studies compared outcomes from participants taking two antidepressants together with those taking either a single antidepressant at 'standard' dose (with or without placebo) or a single antidepressant at 'high' dose (with or without placebo). The following combinations were possible:

- SSRIs ('standard' dose) plus mianserin versus SSRIs ('standard' dose) (FERRERI2001, LICHT2002, MAES1999)

- Various antidepressants ('standard' dose) plus mirtazapine versus various antidepressants ('standard' dose, with or without placebo) (CARPENTER2002)

- Amitriptyline plus moclobemide versus amitriptyline ('standard' dose, with or without placebo) (TANGHE1997)

- Sertraline (100 mg) plus mianserin versus high dose sertraline (200 mg, alone or with placebo) (LICHT2002)

- Fluoxetine (20 mg) plus desipramine versus high dose fluoxetine (40 mg to 60 mg, alone or with placebo) (FAVA1994, FAVA2002).

In trials comparing two antidepressants with a single antidepressant at 'standard' dose efficacy data were available from up to 353 participants and tolerability data from up to 293 participants. two antidepressants with a single antidepressant at high dose efficacy data were available from up to 390 participants and tolerability data from up to 290 participants.

All included studies were published between 1994 and 2002 and were between four and six weeks long (mean = 4.57 weeks). Two studies were of inpatients (MAES1999, TANGHE1997) and four of outpatients (CARPENTER2002, FAVA1994, FAVA2002, FERRERI2001, LICHT2002) with none in primary care. Participants in FERRERI2001 were from mixed sources. No study included all older participants or those with atypical features.

The studies were analysed three ways: all available trials, acute-phase non-responders only and treatment resistant patients only.

Evidence statements for the complete dataset

Effect of treatment on efficacy

There is some evidence suggesting that there is a clinically significant difference favouring two antidepressants over a single antidepressant (with or without placebo) on:

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N= 3; n= 293; RR= 0.81; 95% CI, 0.67 to 0.97)
- reducing depression symptoms by the end of treatment as measured by the HRSD or the MADRS (N= 5; n= 353; Random effects: SMD= -0.53; 95% CI -0.97 to -0.10).

There is insufficient evidence to determine whether there is a clinically significant difference between two antidepressants over a single antidepressant (with or without placebo) on achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N= 4; n= 316; Random effects: RR= 0.66; 95% CI, 0.43 to 1.02).

There is insufficient evidence to determine whether there is a clinically significant difference between two antidepressants and a single high dose antidepressant (with or without placebo) on any efficacy measure.

Acceptability of treatment

There is some evidence suggesting that, on reducing the likelihood of patients reporting side effects, there is a clinically significant difference favouring:

- a single antidepressant (with or without placebo) over two antidepressants (N= 1; n= 197; RR= 1.68; 95% CI, 1.32 to 2.14)
- a single high dose antidepressant (with or without placebo) over two antidepressants (N= 1; n= 196; RR= 1.39; 95% CI, 1.13 to 1.71).

There is insufficient evidence to determine if there is a clinically significant difference between either two antidepressants and a single antidepressant (with or without placebo) or between two antidepressants and a single high dose antidepressant (with or without placebo) on other tolerability measures.

Evidence statements for acute-phase non-responder trials

Effect of treatment on efficacy

In patients who have failed one course of antidepressants there is some evidence suggesting that there is a clinically significant difference favouring two antidepressants over a single antidepressant (with or without placebo) on increasing the likelihood of achieving remission (N= 3; n= 293; RR= 0.81; 95% CI, 0.67 to 0.97).

In patients who have failed one course of antidepressants there is insufficient evidence to determine if there is a clinically significant difference between two antidepressants and a single antidepressant (with or without placebo) on achieving a 50% reduction in depression symptoms or on reducing depression symptoms or between two antidepressants and a single high-dose antidepressant (with or without placebo) on any efficacy measure.

Acceptability and tolerability of treatment

In patients who have failed one course of antidepressants, there some evidence suggesting that there is a clinically significant difference favouring:

- a single antidepressant (with or without placebo) over two antidepressants on reducing the likelihood of patients reporting side effects (N= 1; n= 197; RR= 1.68; 95% CI, 1.32 to 2.14)
- a single high-dose antidepressant (with or without placebo) over two antidepressants on patients reporting side effects (N= 1; n= 196; RR= 1.39; 95% CI, 1.13 to 1.71).

In patients who have failed one course of antidepressants, there is insufficient evidence to determine if there is a clinically significant difference between either two antidepressants and a single antidepressant (with or without placebo) or between two antidepressants and a single high-dose antidepressant (with or without placebo) on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

Evidence statements for treatment resistant trials

Effect of treatment on efficacy

In treatment resistant patients there is some evidence suggesting that there is a clinically significant difference favouring two antidepressants over a single antidepressant (with or without placebo) on:

- achieving a 50% reduction in depression symptoms (N= 1; n= 18; RR= 0.34; 95% CI, 0.13 to 0.92)
- reducing depression symptoms (N= 2; n = 57; Random effects: SMD = -0.99; 95% CI , -1.87 to -0.1).

Acceptability of treatment

There is no evidence on the acceptability of treatment in treatment resistant patients.

Clinical summary

In a mixed population of patients there is some evidence that augmenting one antidepressant with another leads to better outcomes on response, remission and mean endpoint scores compared to a single antidepressant at 'standard' dose. There is insufficient evidence to determine whether this is the case when compared to a single antidepressant at high dose.

Since the majority of studies used mianserin as the augmentor, the analyses are weighted towards this drug. Importantly, there are no studies of combinations of a TCA and irreversible MAOI or any two from venlafaxine, mirtazapine and reboxetine.

There is some evidence that combinations of antidepressants are associated with a higher burden of side effects than a single antidepressant at either standard or high dose, but there is insufficient evidence to comment of the number of patients leaving treatment early.

Where there was sufficient evidence similar results were found when trials of acute-phase non-responders and treatment resistant patients were analysed separately.

8.3.4.4 Augmenting an antidepressant with pindolol

Serotonergic antidepressants inhibit the reuptake of serotonin into the presynaptic neurone thus increasing serotonergic neurotransmission. The immediate effect of this increase is to stimulate serotonin 1a autoreceptors which results in a decrease in serotonin release. In time, these autoreceptors become desensitised and serotonin release returns to normal. This, in combination with the inhibition of serotonin reuptake, is though to lead to the onset of antidepressant effect.

Pindolol is primarily an adrenergic b-blocking drug which also blocks serotonin 1a autoreceptors. The co-administration of pindolol with a serotonergic antidepressant could be expected to result in an immediate increase in serotonin neurotransmission, thus eliminating the delay in onset of antidepressant response.

As well as being used to speed the onset of antidepressant response, pindolol has also been used to augment the efficacy of antidepressant drugs in acute phase non-responders and treatment resistant depression.

Studies considered for review

Twenty-four studies were found in a search of electronic databases, six of which met the inclusion criteria set by the GDG (BORDET1998, MAES1999, PEREZ1997, PEREZ1999, TOME1997, ZANARDI1997) and 18 of which did not.

Only studies comparing pindolol plus an antidepressant with pindolol plus placebo were included in the analyses. Apart from one study (PEREZ1999) which included clomipramine as well as a range of SSRIs, all studies used a single SSRI as the antidepressant. Efficacy data were available from up to 282 participants and tolerability data from up to 333 participants.

All included studies were published between 1987 and 1999 with participants being randomised to an experimental treatment phase of between ten days and six weeks (mean = 4.25 weeks).

In two studies participants were described as inpatients (MAES1999, ZANARDI1997), in a further two as outpatients (PEREZ1999, TOME1997), in one as primary care (PEREZ1997) and in the remaining trial participants were from mixed sources (BORDET1998). In no trial were participants exclusively older or had atypical features. The mean dose of pindolol was 9.23 mg, ranging from 7.5 mg to 15 mg.

No trial was classified acute-phase non-responder, and only one was classified treatment resistant (PEREZ1999). Here patients were randomised to receive augmentation for ten days with either pindolol (7.5 mg) or placebo after receiving fluoxetine (40 mg), fluvoxamine (200 mg), paroxetine (40 mg) or clomipramine (150 mg) for at least six weeks beforehand. In addition participants had already failed between one and four courses of antidepressants (median two). Most patients were outpatients aged 18 to 65. Results from a separate analysis of this trial are presented below.

Outcomes are classified according to when assessment measures were taken. Up to 14 days after treatment was begun was categorised 'early assessment point' and more than 20 days was categorised 'late assessment point'. Three studies (TOME1997, BORDET1998, ZANARDI1997) gave outcomes at both assessment points.

Evidence statements

Effect of treatment on efficacy

Early assessment point

There is evidence suggesting that there is no clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on achieving a 50% reduction in depression symptoms by the 10th day of treatment (N= 2; n= 160; RR= 0.95; 95% CI, 0.82 to 1.11).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on:

- increasing the likelihood of achieving remission by the 10th or 14th day of treatment (N= 3; n= 222; Random effects: RR= 0.73; 95%CI, 0.44 to 1.20)
- reducing depression symptoms by the 10th to 14th day of treatment (N= 3; n= 237; Random effects: SMD= -0.30; 95%CI, -0.88 to 0.28).

Late assessment point

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on achieving a 50% reduction in depression symptoms by the 35th or 42nd day of treatment (N= 3; n= 214; RR= 0.75; 95% CI, 0.54 to 1.03).

There is some evidence suggesting that there is a clinically significant difference favouring SSRIs plus pindolol over SSRIs plus placebo on increasing the likelihood of achieving remission by the 21st, 28th or 42nd day of treatment (N= 3; n= 253; RR= 0.73; 95% CI, 0.55 to 0.98).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs plus pindolol over SSRIs plus placebo on reducing depression symptoms by the 21st, 35th or 42nd day of treatment, but the size of this difference is unlikely to be of clinical significance (N= 4; n= 282; SMD= -0.26; 95% CI, -0.49 to -0.02).

Acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on any measure of tolerability.

Effect of treatment on efficacy for treatment resistant patients

Early assessment point

For treatment resistant patients there is evidence suggesting that there is no clinically significant difference when assessment is made between days 10 and 14 between pindolol augmentation and antidepressant monotherapy on:

- achieving a 50% reduction in depression symptoms (N= 1; n= 80; RR= 1; 95% CI, 0.85 to 1.18)
- increasing the likelihood of achieving remission (N= 1; n= 80; RR= 1.03; 95% CI, 0.88 to 1.2).

There is insufficient evidence to determine if there is a clinically significant difference between pindolol augmentation and antidepressant monotherapy on reducing depression symptoms in treatment resistant patients (N= 1; n= 80; WMD= 1.6; 95% CI, -0.96 to 4.16).

Acceptability of treatment for treatment resistant patients

There are no data on the acceptability of treatment for treatment resistant patients.

Clinical summary

While there is some evidence of an advantage (at 21-42 days) favouring the addition of pindolol to antidepressants over adding placebo on achieving remission, this effect is not evident for response or mean endpoint scores. There is no evidence of any effect on outcomes in purely treatment resistant patients at early assessment point. No data were available for late assessment points.

There is insufficient evidence to comment on the tolerability of adding pindolol to antidepressants.

It should be noted that there is uncertainty regarding optimum dose and duration of treatment.

8.3.4.5 Augmenting an antidepressant with triodothronine (T3)

Consistent with the observations that the prevalence of depression is increased in hypothyroidism (Loosen, 1987) and subclinical hypothyroidism is more prevalent in people who are clinically depressed (Maes et al, 1993), triodothronine (T3) has been used as an antidepressant augmenting agent both to increase the speed of onset of antidepressant response and to increase the magnitude of response.

Increase the speed of onset of antidepressant response

T3, at a dose of 25mcg per day may hasten response to tricyclics and this effect may be more robust in women (Altshuler et al, 2001). The optimal duration of treatment is unknown although there is a suggestion in the literature that T3 may be safely withdrawn once response has been achieved (Altshuler et al, 2001). There are no studies with SSRIs or any of the newer antidepressants.

Increase the magnitude of antidepressant response

Although the RCT which satisfied the inclusion criteria set by the GDG that found T3 and lithium to be equally effective and superior to placebo (see below), several 'negative' non-RCTs also exist (Steiner et al, 1978, Gitlin et al, 1987, Thase et al, 1989). The response rate has been variable across studies (Aronson et al, 1996). All studies used tricyclic antidepressants. There are no studies with SSRIs or any of the newer antidepressants. T4 has been shown to be inferior to T3 in one study (Joffe & Singer, 1990). Most studies used a dose of 37.5mcg T3 per day. The optimum duration of treatment is unknown.

Studies considered for review

One study was found in a search of electronic databases (JOFFE1993A), and this met the inclusion criteria set by the GDG. It compares a range of antidepressants augmented with T3 (37.5µg) with antidepressants augmented with placebo. Participants are outpatients who have not achieved remission after five weeks' treatment with either desipramine or imipramine.

Evidence statements

Effect of treatment on efficacy outcomes

There some evidence suggesting that there is a clinically significant difference favouring T3 augmentation over antidepressant plus placebo on achieving a 50% reduction in depression symptoms (N= 1; n= 33; RR= 0.51; 95% CI, 0.27 to 0.94)).

There is insufficient evidence to determine if there is a clinically significant difference between T3 augmentation and antidepressant plus placebo on reducing depression symptoms (N= 1; n= 33; WMD= -3.9; 95% CI, -8.86 to 1.06).

Acceptability of treatment

There was no evidence on which to assess the acceptability of treatment.

Clinical summary

There is little evidence on which to make an evidence-based recommendation of augmentation of antidepressants with T3 for the treatment of refractory depression. The prevalence of cardiovascular disease is increased in people with depression (Glassman & Shapiro, 1998) and T3 should be used with caution in cardiovascular disease. Potential adverse effects include tachycardia, anginal pain and arrhythmias. Tricyclic antidepressants also have cardiac side effects including arrhythmias, tachycardia and postural hypotension. Caution is advised in combining TCAs and T3.

8.3.4.6 Augmenting an antidepressant with a benzodiazepine

Introduction

Depression and anxiety commonly co-exist and insomnia is a core symptom of depression. Antidepressants usually take two to four weeks to take effect.

Benzodiazepines are effective anxiolytic and hypnotic drugs with an immediate onset of action and therefore could be expected to produce early improvement in some symptoms of depression. They do not have a specific antidepressant effect.

Benzodiazepines are associated with tolerance and dependence and withdrawal symptoms can occur after 4-6 weeks of continuous use. To avoid these problems, it is recommended that they should not routinely be prescribed for their hypnotic or anxiolytic effects for longer than four weeks (Royal College of Psychiatrists, 1997; BNF, 2003).

The National Service Framework for mental health (NSF, 1999) discourages the use of benzodiazepines and many primary care prescribing incentive schemes include low prescribing rates for benzodiazepines as a marker of good practice. A Cochrane review however, concludes that early time limited use of

benzodiazepines in combination with an antidepressant drug may accelerate treatment response (Furukawa et al., 2002).

Studies considered for review

The GDG used an existing review (Furukawa et al., 2002) as the basis for this section. The original review included nine studies of which four were met the inclusion criteria set by the GDG (FEET1985, NOLEN1993, SCHARF1986, SMITH1998). New searches of electronic databases found an additional study (SMITH2002) which was included in the present review. Together these studies provided tolerability data from up to 196 participants and efficacy data from up to 186 participants.

All included studies were published between 1985 and 2002 and were between three and twelve weeks long (mean = 7 weeks). One study was of inpatients (NOLEN1993), three of outpatients (FEET1985, SMITH1998, SMITH2002) and in the remaining study (SCHARF1986) participants were from mixed sources. No study was undertaken in primary care, nor was any of exclusively older participants or those with atypical features. Other than in FEET1985, where participants had been 'treated in general practice without success', study participants were not described as having failed previous courses of antidepressants.

All studies compared an antidepressant plus benzodiazepine with an antidepressant plus placebo. The included trials used the following antidepressant/benzodiazepine combinations:

- Maprotitline or nortriptyline plus flunitrazepam (2 mg) or lormetazepam (2 mg) (NOLEN1993)
- Fluoxetine plus clonazepam (0.5 mg up to 1 mg) (SMITH1998, SMITH2002)
- Imipramine plus diazepam (10 mg) (FEET1985)
- Amitriptyline plus chlordiazepoxide (mean 44 mg) (SCHARF1986)

The mean dose of TCAs was between 122.5 mg and 200 mg, and fluoxetine was given at between 20 mg and 40 mg.

Evidence statements

Effect of treatment on efficacy

There is insufficient evidence to determine whether there is a clinically significant difference between antidepressants plus a benzodiazepine and antidepressants plus placebo on any efficacy measure.

Acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between antidepressants plus a benzodiazepine and antidepressants plus placebo on any tolerability measure.

Clinical summary

There is insufficient evidence to determine whether there is any effect of adding a benzodiazepine to antidepressant treatment in terms of both efficacy and tolerability.

8.3.4.7 Augmenting antidepressants with an antipsychotic

Introduction

Ostroff and Nelson (1999) reported on eight patients with non-psychotic depression who had failed to respond to an SSRI did respond when risperidone was added. In an eight-week, double-blind clinical trial of olanzapine in combination with fluoxetine in patients who were 'stage two treatment resistance', the combination was superior to either agent on its own (Tohen et al., 1999).

Studies considered for review

A separate search for systematic reviews of antipsychotic augmentation of antidepressants was undertaken (i.e., in addition to the searches undertaken for all systematic reviews for the treatment of depression – see Chapter 3). Since no suitable review was found, the GDG took the decision to search for RCTs only for olanzapine augmentation of fluoxetine. One study was found in a search of electronic databases (SHELTON2001), and this met the inclusion criteria set by the GDG. It compares fluoxetine plus olanzapine with fluoxetine plus placebo. Patients had failed at least two courses of antidepressants before entering the study, and were randomised to augmentation treatment only if they failed to respond to a course of open-label fluoxetine.

Evidence statements

Effect of treatment on efficacy outcomes

There some evidence suggesting that there is a clinically significant difference favouring augmentation of fluoxetine with olanzapine over fluoxetine alone on achieving a 50% reduction in depression symptoms (N= 1; n= 20; RR= 0.44; 95% CI, 0.2 to 0.98).

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between augmentation of fluoxetine with olanzapine and fluoxetine alone on reducing the likelihood of leaving treatment early (N= 1; n= 20; RR= 0.33; 95% CI, 0.04 to 2.69).

Clinical summary

There is little evidence on which to make an evidence-based recommendation of antipsychotic augmentation of antidepressants for the treatment of refractory depression.

8.3.4.8 Augmenting an antidepressant with buspirone

Introduction

Buspirone is a 5HT1a partial agonist that is licensed for the treatment of anxiety. Its proposed mechanism of action as an augmentor of antidepressant drugs is similar to that of pindolol (see section 8.3.4.4).

Studies considered for review

Only studies comparing antidepressant augmentation with buspirone with augmentation with placebo were considered. One study was included (APPELBERG01). This compared fluoxetine or citalopram augmented with buspirone (20 mg to 60 mg) with antidepressants augmented with placebo.

Evidence statements

Effect of treatment on efficacy

There are no extractable data on the efficacy of buspirone augmentation.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between buspirone augmentation and SSRI monotherapy on any tolerability measure.

Clinical summary

There is no evidence on which to make an evidence-based recommendation of augmentation of antidepressants with buspirone for the treatment of refractory depression.

8.3.5 Recommendations for the pharmacological treatment of refractory depression

8.3.5.1.1 Where combinations of antidepressants other than mianserin with SSRIs and mirtazapine with SSRIs are considered, healthcare professionals should re-evaluate the adequacy of previous treatments carefully before proceeding and consider seeking a second or specialist opinion. The content of any discussion should be documented in the notes. (C)

8.3.5.1.2 Where patients are treated with one antidepressant augmented by another, careful monitoring of the treatment is advised and the importance of this should be explained to the patient. (GPP)

8.3.5.1.3 In patients whose depression has failed to respond to a single antidepressant, the addition of lithium could be beneficial but is associated with significant side effects and risk of toxicity. (C)

8.3.5.1.4 There is insufficient evidence to recommend the use of benzodiazepine augmentation of antidepressants. (C)

8.3.5.1.5 Augmenting an antidepressant with another antidepressant should be considered for patients whose depression is treatment resistant and who are prepared to tolerate the side effects. There is evidence for the benefits of the addition of mianserin or mirtazapine to SSRIs. (C)

8.3.5.1.6 When used to augment another antidepressant mianserin should be used with caution particularly in older adults because of the risk of agranulocytosis. (C)

8.3.5.1.7 When considering alternatives to SSRIs, venlafaxine may be considered for those who have failed two adequate trials of alternative antidepressants. The dose can be increased up to BNF limits if required, provided patients can tolerate the side effects. (C)

8.3.5.1.8 In patients whose depression has failed to respond to several antidepressants a trial of lithium augmentation should be considered in patients who are prepared to tolerate the burdens associated with its use. (B)

8.3.5.1.9 In secondary care phenelzine should be considered for those patients who have failed to respond to alternative antidepressants and who are

prepared to tolerate the side effects and dietary restrictions associated with its use. (C)

8.3.5.1.10 Augmentation of an antidepressant with carbamazepine, lamotrigrine, buspirone, pindolol, valproate or thyroid supplementation is not recommended in the routine management of treatment resistant depression. (B)

8.3.6 Research recommendations

An adequately powered RCTs reporting all relevant outcomes should be undertaken to assess the efficacy of valproate and lamotrigine in the management of treatment resistant depression.

9 Health economics evidence

9.1 Background

In order to help the decision-making process of the GDG, relevant economic evidence was collected and assessed where available. This process was based on a preliminary analysis of the clinical evidence and had three stages:

- Identification of the areas with likely major cost impacts within the scope of the guideline;
- Systematic review of existing data on the economic burden of major depressive disorder and cost-effectiveness evidence of different treatment options for depression;
- Primary economic evaluation alongside the guideline development procedure to provide cost-effectiveness evidence where such previous data did not exist.

9.2 Key economic issues

The GDG, in collaboration with the health economist, identified four key economic issues relevant to the management of major depressive disorder in the UK:

- The economic burden of depression in the UK
- Comparative cost-effectiveness of older versus newer antidepressants
- Comparative cost-effectiveness of relapse prevention with maintenance antidepressant treatment versus no maintenance antidepressant treatment for relapse prevention
- Comparative cost-effectiveness of pharmacological, psychological and combination therapies for patients with depression treated in primary or secondary care.

9.3 Systematic literature review

A systematic review of the health economic evidence was conducted. The aim was three-fold:

- To identify all publications with information about the economic burden of depression in the UK;
- To identify existing economic evaluations of any psychological, pharmacological, or other physical or service level interventions for the treatment of major depressive disorder undertaken in the UK; and

- To find studies with health state utility evidence generalisable to the UK context to facilitate a possible cost-utility modelling process.

Although no attempt was made to review systematically studies with only resource use or cost data, relevant UK-based information was extracted for future modelling exercises if it was considered appropriate.

9.3.1 Search strategy

In September 2002, bibliographic electronic databases (Medline, PreMedline, Embase, CINAHL, PsycINFO, CDSR, CCTR, DARE, HTA) and specific health economic databases (NHS EED, OHE HEED) were searched for economic studies. For Medline, PreMedline, Embase, CINAHL, PsycINFO, CDSR, CCTR and DARE, a combination of a specially developed health economics search filter already tested in earlier NCCMH guidelines and a general filter for major depressive disorder was used. A combination of subject headings and free-text searches was used. HTA, NHS EED and OHE HEED were searched using shorter, database-specific strategies. OHE HEED was searched again in April 2003 to identify recently published economic studies.

Applying similar methodology, secondary searches, focused on a selection of antidepressants chosen as 'class markers', were carried out to identify additional pharmacoeconomic studies. Search strategies and further information are presented in Appendix 14.

In addition to searches of electronic databases, reference lists of eligible studies and relevant reviews were searched by hand, and experts in the field of depression and mental health economics were contacted to identify additional relevant published and unpublished studies. Studies included in the clinical evidence review were also screened for economic evidence.

9.3.2 Review process

The database searches for general health economic evidence for depression resulted in a total of 8,570 references. Of these, 1,669 were identified as potentially relevant. Secondary searches for additional pharmacoeconomic papers resulted in 1,156 references, of which, 63 were initially considered relevant. A further 50 potentially eligible references were found by handsearching. A second sift of titles/ abstracts by the health economist reduced the overall number of potentially relevant publications to 353. (At this stage inclusion was not limited to papers only from the UK.) Full texts of all potentially eligible studies (including those where relevance/eligibility was not clear from the abstract) were obtained. These publications were then assessed against a set of standard inclusion criteria by the health economist, and papers eligible for inclusion as economic evaluations were subsequently assessed for internal

validity. The quality assessment was based on the 32-point checklist used by the British Medical Journal to assist referees in appraising economic analyses (Drummond & Jefferson, 1996) (Appendix 15).

9.3.3 Selection criteria

Cost-of-illness/ economic burden studies

- There was no restriction placed on language or publication status of the papers.
- Studies published between 1980 and 2003 were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.
- Only studies from the UK were included, as the aim of the review was to identify economic burden information relevant to the national context.
- Selection criteria based on types of clinical conditions and patients were identical to the clinical literature review (see Appendix 8).
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable.

Economic evaluations

- Studies were included provided they had used cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis.
- Clinical evidence from a meta-analysis, a randomised controlled trial, a quasi-experimental trial or a cohort study was used.
- There was no restriction placed on language or publication status of the papers.
- Studies published between 1980 and 2003 were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.

- Only studies from the UK were considered, as the aim of the review was to identify economic evaluation information relevant to the national context.

- Selection criteria based on types of clinical conditions, patients, treatments and settings were identical to the clinical literature review (see Appendix 8).

- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable.

Health state utility studies

- Studies reporting health state utilities for depression were considered for inclusion.
- There was no restriction placed on language or publication status of the papers.
- Studies published between 1980 and 2003 were included.
- Only studies from OECD countries were considered to assure the generalisability of the results to the UK context.

- Selection criteria based on types of clinical conditions, patients, treatments and settings were identical to the clinical literature review (see Appendix 8).

9.3.4 Data extraction

Data were extracted by the health economist. Masked assessment, whereby data extractors are blind to the details of journal, authors, etc., was not undertaken because there is no evidence to support the claim that this minimises bias (Cochrane, 2001).

9.3.5 Evidence synthesis

9.3.5.1 Cost-of-illness/economic burden studies

Altogether, 12 publications were deemed eligible for a review of the economic burden of depression (Berto et al., 2000; West, 1992; Kind & Sorensen, 1993; Jonsson & Bebbington, 1993; Eccles et al., 1999; Freemantle & Mason, 1995; Freemantle et al., 1998; Lepine et al., 1997; Goldberg et al., 1996; Hughes et al., 1997; Knapp & Ilson, 2002; Henry, 1993). This is presented in Chapter 3.

9.3.5.2 Economic evaluations

Not counting multiple publications, 26 papers were selected for data abstraction. Details and results of the included studies are summarised in the form of an evidence table in Appendix 16. Only a short summary of the results is reported here.

Pharmacological interventions

Two studies addressed the cost-effectiveness of maintenance antidepressant therapy (Hatziandreu et al., 1994; Kind & Sorensen, 1995). Kind and Sorensen (1995) compared maintenance antidepressant therapy with the 'watchful waiting approach'. Although the average cost per symptom-free patient was higher for maintenance therapy, the cost difference was minor. The incremental analysis by Hatziandreu et al. (1994) confirmed that maintenance therapy is cost-effective compared to acute episodic treatment.

One study with moderate internal validity compared the use of an augmentor (pindolol) vs. placebo with SSRI treatment (Tome 1998). The average effectiveness-cost ratio favoured the augmentation treatment option.

Ten papers investigated the comparative cost-effectiveness of newer versus older antidepressants (Borghi & Guest, 2000; Doyle et al., 2001, Freemantle et al., 1994; Freeman et al., 2000; Forder et al., 1996; Jonsson & Bebbington, 1994; Montgomery et al., 1996; Stewart,1994; Stewart, 1996; Woods & Rizzo, 1997), one of which was an update of an earlier calculation (Stewart, 1996) and another one (Woods & Rizzo, 1997) was a reassessment of the model by Jonsson and Bebbington (1994) . Apart from the study by Borghi and Guest (2000) all used modelling techniques for their estimations.

The result of the paper by Freemantle et al. (1994) did not support the first-line use of newer antidepressants, the earlier study by Stewart (1994) could not show any cost advantage of SSRIs over TCAs, and the reassessed cost-effectiveness analysis by Woods and Rizzo (1997) did not confirm the superiority of paroxetine over imipramine showed earlier by Jonsson and Bebbington (1994).

The other seven studies showed that SSRIs are more cost effective than TCAs. Out of these, the study by Montgomery et al. (1996) was based on the same model as the analysis of Jonsson and Bebbington (1994) but used a different SSRI as the comparator. There were a further two studies which were based on identical models (Doyle et al., 2001, Freeman et al., 2000). These two studies also compared venlafaxine to SSRIs and TCAs and concluded that venlafaxine is more cost effective than older antidepressants. However, the clinical estimates used for these comparisons were inconsistent with the results of our clinical

evidence review. Hence, an opportunity cost approach was taken and information on the four-month primary care cost (medication , staff, dispensing) of different antidepressant treatments was considered alongside the clinical evidence (Table 1). Resource use information used for the cost calculations was obtained from the GDG acting as an expert panel.Unit cost data were extracted from multiple sources (BNF, 2003; Netten et al., 2002). All costs were expressed in 2003 £.

Table 1. Antidepressant therapy cost

Antidepressant	***Average daily dose (mg)***	***Treatment cost per patient (£, 2003)***
amitriptyline	75	70.06
imipramine (NP)	100	76.90
lofepramine (Gamanil)	140	101.79
citalopram	20	128.32
fluoxetine (NP)	20	90.06
paroxetine (NP)	20	118.90
phenelzine (Nardil)	45	131.44
reboxetine (Edronax)	8	135.26
sertraline (Lustral)	100	173.23
moclobemide (NP)	300	135.06
mirtazapine (Zispin)	30	157.89
venlafaxine (Efexor)	100	196.59

Summary:

Based on the published information and on recent clinical evidence showing significantly better outcomes with maintenance therapy, it is likely that

antidepressant maintenance therapy is cost-effective to prevent relapse. However, no health economic evidence exists about the optimal length of maintenance therapy.

Current pharmacoeconomic evidence suggests that SSRIs are more cost-effective than TCAs for the first-line treatment of major depression. In opposite, the result of our clinical evidence review together with the opportunity cost considerations did not support the first-line use of venlafaxine in comparison with SSRIs.

Unfortunately, the published evidence is not sufficient to inform present guideline recommendations on the single most cost-effective antidepressant for the first-line treatment of major depression in the UK. The availability of resources for the guideline development process did not permit primary modelling of such evidence. In the future, a comprehensive, independent model of the evidence on the cost-effectiveness of newer antidepressants used as first-line treatments is necessary. This should take into consideration that prices of the newer antidepressants are likely to decrease significantly in the near future as generic versions of proprietary drugs become available.

Psychological interventions

Eight studies focused on the cost-effectiveness of brief psychological interventions or computerised CBT in primary care compared to usual GP care (Miller et al., 2003, Simpson et al., 2000; Friedli et al., 2000; King et al., 2000; Mynors-Wallis et al., 1997; McCrone et al., 2003; Kaltenthaler et al., 2002, Scott & Freeman 1992). Four studies could not find a significant difference either in the outcomes or in the costs between the different alternatives (Miller et al., 2003; Simpson et al., 2000; Friedli et al., 2000; King et al., 2000). The cost-effectiveness estimate of Mynors-Wallis et al. (1997) favoured usual GP care when a healthcare perspective was used, and found problem solving therapy provided by community nurses superior in the societal perspective. Scott and Freeman (1992) found counselling provided by social workers more effective than usual GP care, but usual GP care was less costly than any of the specialist treatments assessed in the study (amitriptyline prescribed by a psychiatrist, CBT, counselling). However, due to the small sample sizes of the latter two studies, no firm conclusions can be drawn from these results. One study, not yet published, found computerised CBT superior to routine care (McCrone et al., 2003). A recent Health Technology Assessment supports this finding, but the authors state that these estimates are crude and should be treated with caution (Kaltenthaler et al., 2002). They also estimated great differences in the cost-effectiveness of the different types of computerised CBT. In summary, it is likely that the additional costs of brief psychological interventions provided in primary care are offset by savings on other healthcare costs. Hence, other factors such as clinical benefits,

patient preferences and staff availability should be taken into consideration when choosing between these alternatives (King et al., 2000).

Three further studies investigated the cost-effectiveness of psychological interventions on an outpatient basis. The study by Leff et al. (2000) showed that couples therapy was superior to antidepressant therapy in terms of clinical outcomes and that the additional costs of couples therapy were offset by savings in other health service use. However, the validity of the results is greatly limited due to the high drop out rate. For the same reason, the study was excluded from the clinical review. The study by Guthrie et al. (1999) compared brief psychodynamic interpersonal therapy to usual psychiatrist care. They found psychotherapy to be both more effective and cost saving. A recent study by Scott et al. (2003) reported that CBT in combination with antidepressant therapy is likely to be cost-effective for patients with residual depression.

Electroconvulsive therapy (ECT)

A recent Health Technology Appraisal (NICE, 2003) could not identify any published economic studies relating to ECT. The primary model constructed by the Assessment Group concluded that ECT and pharmacotherapy are likely to be equally cost-effective for the inpatient treatment of adults with severe depression. The authors highlight that considerable amount of uncertainty exists in the data on which the model was based.

Service provision

One study assessed the efficiency of service provision in hospital or in the community (Goldberg et al., 1996). Using less robust economic methodology, the authors found the latter alternative significantly cost saving, while no difference could be detected between the two options in terms of clinical outcome.

9.3.5.3 Health state utility studies

Among the studies already assessed for eligibility, six publications could be identified reporting information relevant to patient-assigned health state utility values for depression (Bennett et al., 2000; King et al., 2000; Pyne et al., 1997; Pyne et al., 2001; Revicki & Wood, 1998; Whalley & McKenna, 1995).

The paper by Whalley and McKenna (1995) summarised the different quality-of-life instruments for depression and anxiety, and reviewed published studies of quality-of-life in depression and anxiety. They concluded that very few published studies were available on the topic at that time. King et al. (2000) based their estimates on a patient population with mixed anxiety/depression and so these utility values were not suitable to inform a possible cost-utility model for patients with depression only. The paper by Bennett et al. (2000) presented a

specific utility measure for depression health states and so its result could not be used to calculate Quality-Adjusted-Life-Years (QALYs), which would be comparable across different disease areas. Neither the study from 1997 (Pyne et al., 1997) nor the result of a more recent study by Pyne et al. (Pyne et al., 2001) provided sufficient information for the calculation of QALYs for economic analyses. The earlier study showed that there is a highly significant reduction in the Quality of Well-Being scale (QWB) scores for people with MDD compared to controls and that the scores are inversely correlated with depression severity (Pyne et al., 1997). The latter study revealed that although the overall index score of the QWB scale was not a strong predictor of acute treatment response to inpatient antidepressant therapy, the lower scores on the physical activity and the higher scores on the social activity subscales of QWB are among the strongest predictors of such response (Pyne et al., 2001). The health state utility values reported by Revicki and Wood (1998) however were deemed suitable to be used for the calculation of QALYs for our model.

Summary:

All six studies reported significant impact of depression on the quality-of-life of patients with major depressive disorder (MDD). People with moderate to severe depression had QWB scores similar to ambulatory AIDS patients and patients with moderate to severe chronic obstructive pulmonary disease (Pyne et al., 1997). A considerable proportion (25%) of the patients with MDD valued the state of severe depression worse than death or equal to death (Revicki & Wood, 1998). The robustness of these data however needs to be treated with caution due to an ongoing debate about the sensitivity and reliability of utility measures for patients with mental health problems (Chisholm et al., 1997). In the lack of several comparable studies investigating this question in patients with major depression, significant uncertainty remains around the current estimates.

9.4 Cost-effectiveness modelling

9.4.1 Background

The literature search did not identify any robust existing evidence on the comparative cost-effectiveness of individual psychological therapies with pharmacological treatment and the combination of these therapies for patients with depression treated in secondary care. The only study (Scott, 2003) addressing this question was published only recently and had limited generalisability as it was based on a patient group with residual depression. As a consequence, it was decided to devise a cost-effectiveness model that summarised the available clinical evidence and combine it with relevant cost data to answer the question outlined above.

To conduct an economic evaluation it is necessary to have comparative evidence on the clinical effectiveness of interventions. Of the individual psychological interventions only cognitive behaviour therapy (CBT) had sufficient comparative clinical evidence to undertake an economic evaluation. There was not enough evidence to assess other effective psychological interventions such as interpersonal psychotherapy (IPT). There was also comparative evidence available on antidepressant therapy and antidepressant therapy combined with CBT and therefore these strategies were also assessed.

9.4.2 Methods

Treatment strategies and model structure

A formal decision analytic model was constructed in order to explore the incremental cost-effectiveness of antidepressant therapy and the combination of antidepressant therapy and CBT for the treatment of moderate/severe depression in secondary care. The analysis was undertaken using Microsoft Excel XP. The detailed structure of the decision tree is presented in ***Figure 1***.

Strategy A: antidepressant treatment given for 12 weeks and 12-month follow-up without maintenance treatment (AD)

Strategy B: combination of 12 weeks' antidepressant treatment and 16 sessions of CBT and 12-month follow-up without maintenance treatment (COMB)

Originally three specific strategies for the management of depression were considered. However, the clinical evidence review showed no overall superiority for CBT alone on treatment outcomes over antidepressants. The efficacy evidence together with the significantly higher treatment cost of CBT compared with the cost of antidepressants resulted in the exclusion of CBT alone from the final cost-effectiveness analysis.

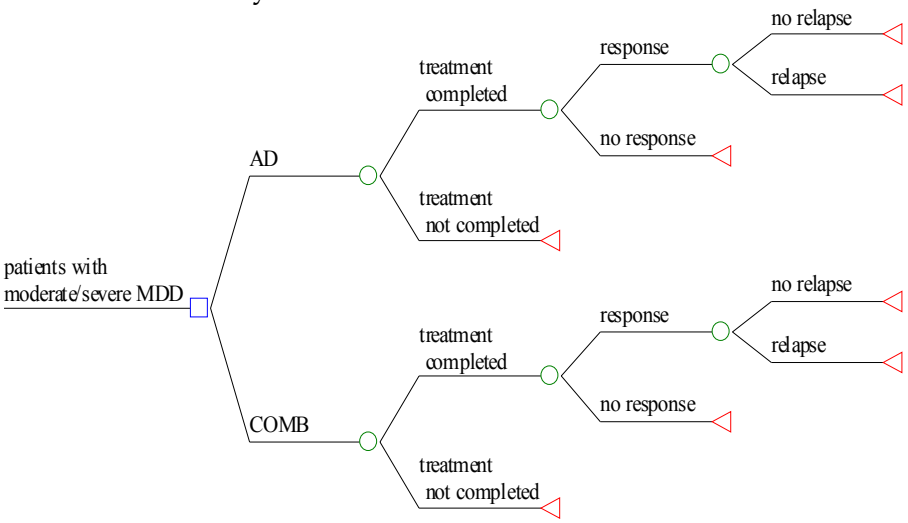

***Figure 1*. Structure of the model**

Assumptions of the model

Population

- A cohort of 100 patients in each arm.
- Each patient in the model has moderate/severe depression and is treated in secondary care.

Antidepressant therapy

- Antidepressant therapy: 40mg/day generic fluoxetine for 12 weeks.
- 'Standard care' is assumed to be antidepressant therapy initiated by a consultant psychiatrist and maintained by a specialist registrar. Initial prescription is for a 2-weekly dose of the medication followed by prescriptions of doses for six and four weeks. There are four consultations, each lasting 15 minutes on average.
- Intensive clinical management means weekly sessions of 20 minutes for 12 weeks provided by the psychiatrist.
- The outcome of antidepressant therapy does not depend on whether standard care or intensive clinical management is provided. (The clinical evidence was based on a mixture of studies using formal clinical management or standard GP care in addition to antidepressant therapy.)
- There is no maintenance therapy.
- Occasionally missed treatment sessions mean that full costs are incurred.
- Those patients who do not complete treatment do not incur the full treatment costs, only a proportion of it corresponding to the mean drop out time. However, they will consume other healthcare resources as a consequence of their depression.
- Average time to drop out is 21 days.

- Patients completing treatment but not responding to it, or relapsing during follow-up, will use further healthcare resources as a consequence of their depression.

- The cost of events such as patients taking an overdose of antidepressants has not been included. The drug protocols used in the two treatment strategies were identical. Hence, it was assumed that such cost would not influence the cost difference between the two strategies significantly.

Combination therapy

- Combination therapy consists of 16 sessions of CBT during 12 weeks, 12 weeks' antidepressant therapy and standard care as described above. One CBT session is 50 minutes in duration. CBT is provided by a suitably qualified and trained clinical psychologist. (In the model, a clinical psychologist was used as a representative example of therapists providing CBT for patients with depression in secondary care.)

- There is no maintenance therapy.

- Occasionally missed treatment sessions mean that full costs are incurred.

- Those patients who do not complete treatment do not incur the full treatment costs, only a proportion of it corresponding to the mean drop out time. However, they will consume other healthcare resources as a consequence of their depression.

- Average time to drop out is 21 days.

- Patients completing treatment but not responding to it, or relapsing during follow-up, will use further healthcare resources as a consequence of their depression.

- The cost of events such as patients taking an overdose of antidepressants has not been included. The drug protocols used in the two treatment strategies were identical. Hence, it was assumed that such cost would not influence the cost difference between the two strategies significantly.

Clinical outcomes and event probabilities

The number of successfully treated patients was chosen as the primary outcome measure in the economic evaluation. However, a secondary analysis was also carried out using Quality-Adjusted Life Years (QALYs) as the outcome measure. No discounting of benefits was applied since the overall time horizon of the analysis was 15 months.

Clinical parameter estimates were collected as part of the clinical evidence review for the guideline. Although more than one outcome measure was used in the clinical effectiveness review; of these, the dichotomous outcome measure of no response defined by scores greater than 6 on the 17-item HRSD or more than 8 on the 24-item HRSD was chosen as being the most appropriate for the cost-effectiveness analysis.

The event probabilities used in the model were based on intention-to-treat rules. For the base case analysis, absolute risk estimates were taken from the guideline meta-analyses. To determine the minimum/maximum values for sensitivity analysis, the absolute risk ratios of antidepressant therapy and the 95% confidence intervals around the relevant risk differences between antidepressant therapy and combination therapy were combined. Full details of the event probabilities used in the model are given in ***Table 1***.

To estimate benefits in terms of QALYs, utility values were obtained from a published study, which reported patient-assigned health state utilities by depression severity and antidepressant medication (Revicki, 1998). (***Table 1***) Uncertainty around these estimates was also explored by sensitivity analysis.

Resource use and unit costs

Since no patient level data were available to calculate costs for the economic evaluation, deterministic costing of the different treatment strategies was carried out. The costs were identified from the perspective of the National Health Service and included all direct medical costs except healthcare costs attributable to antidepressant overdose. Non-health service expenditure and indirect costs were not considered in the analysis. All cost data were for the year 2002/03. As in the case of outcomes, no discounting was applied since the time horizon of the analysis was 15 months.

Resource utilization data were collected as part of the literature review or from the GDG acting as an expert panel. Unit costs were obtained from a variety of sources including the British National Formulary 45 (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2003) and the Personal Social Services Research Unit (Netten et al., 2002). The applied staff unit costs were without qualification costs, but included salary costs, salary oncosts, overheads, capital overheads and ongoing training costs. Estimated resource utilization data were then combined with the relevant unit cost information to give the average

cost associated with each treatment. All treatment costs for patients who left treatment early were adjusted.

The health service cost of depression management for people who discontinue treatment, do not respond to treatment, or relapse, was also included in the economic evaluation (Borghi, 2000). Due to the great uncertainty around the original estimates, this parameter was included in the sensitivity analysis.

Details of all parameters are listed in ***Table 2***.

Table 2. Model parameters

Parameter	Strategy	Base value (mean)	Range (95% CI)	Source
Clinical outcomes				
Probability of not completing treatment	AD	0.30		Guideline meta-analysis
	COMB	0.25		Guideline meta-analysis
Risk difference in not completing treatment		-0.06	0.00 - (-0.12)	Guideline meta-analysis
Probability of no response when treatment is completed	AD	0.57		Calculated using guideline meta-analysis
	COMB	0.38		Calculated using guideline meta-analysis
Risk difference in no response when treatment is completed		-0.19	(-0.08) – (-0.28)	Calculated using guideline meta-analysis
Probability of relapse at 12-month follow-up	AD	0.55		Simons 1986 and Blackburn 1986
	COMB	0.38		Simons 1986 and Blackburn 1986
Risk difference in relapse at 12-month follow-up		-0.18	(-0.12) – (-0.24)	Simons 1986 and Blackburn 1986
Health state utilities				
Severe depression, untreated		0.30	0.23 – 0.37	Revicki 1998
Fluoxetine treatment, no response		0.63	0.58 – 0.68	Revicki 1998
Fluoxetine treatment, response		0.80	0.76 – 0.84	Revicki 1998
Response, no treatment		0.86	0.82 – 0.90	Revicki 1998
Unit costs (all estimates are in prices £ 2002/03)				

Generic fluoxetine 20 mg per pack	£7.61		BNF 45
Dispensing fee per prescription	£0.95		Prescription Pricing Authority
Consultant psychiatrist (cost per hour of patient contact)	£207		Netten et al. 2002
Specialist registrar (cost per hour of patient contact)	£27		Netten et al. 2002
Clinical psychologist (cost per hour of client contact)	£65		Netten et al. 2002
Cost of depression management for patients discontinuing treatment over 5 months	£245	£60 - £600	Borghi 2000

Incremental cost-effectiveness of COMB versus AD therapy

Since COMB therapy was estimated to be both significantly more effective and more costly than AD treatment, the incremental cost-effectiveness of COMB compared with AD was evaluated by assessing the difference in cost per patient receiving either COMB therapy or AD therapy and the difference in effectiveness of each treatment. The difference in effectiveness was primarily measured as the number of additional successfully treated patients. A secondary analysis based on the number of QALYs gained was also carried out. The incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in the expected direct healthcare costs with the difference in the overall effects of the two strategies.

Sensitivity analyses

One-way sensitivity analysis

There was considerable uncertainty about a few parameter estimates used in the model, and the policy implications of point estimates are usually ambiguous. To explore the effect of uncertainty around individual parameters, a one-way sensitivity analysis was carried out whereby a single parameter was varied between its plausible minimum and maximum values while maintaining all remaining parameters at their base value.

Probabilistic analysis

To demonstrate the joint uncertainty around the parameters used in the cost-effectiveness model, a probabilistic analysis was conducted. Using the base case estimates and the minimum/maximum values of the different variables, appropriate distributions were assigned to each parameter included in the sensitivity analysis and Monte-Carlo simulations of the incremental costs and

effects were carried out. More details of the theoretical basis of probabilistic analysis are described in a publication by Briggs and Gray (1999).

9.4.3 Results

Clinical outcomes

The systematic review of the clinical evidence showed that the number of people leaving treatment early is significantly higher for AD than for COMB, absolute risk 0.30 and 0.25 respectively. Furthermore, the probability of no response when completing treatment is also significantly greater for AD (0.55) than for COMB (0.38). The latter values were based on the overall probability of no response at the end of treatment reported in the clinical evidence review using intention-to-treat principles. The overall difference in clinical outcomes further increased when relapse values were also considered because significantly fewer people who responded to the original COMB treatment relapsed during the 12-month follow-up (0.38 vs. 0.55). Altogether the result of the analysis revealed that approximately 15 more patients out of 100 have positive outcomes in the COMB therapy arm than in the AD treatment arm over the 15-month analysis period. The result also favoured COMB therapy over AD when benefits were measured in QALYs. COMB therapy resulted in 10 more QALYs than AD therapy at the end of the 12-month follow-up.

Costs

Antidepressant treatment costs

The total AD therapy cost included medication cost, staff costs and dispensing fees. Multiple scenarios were considered. The first scenario reflected usual clinical practice and revealed that a full course of 12-week antidepressant therapy with standard care would cost on average £162. The second scenario included the costs of intensive clinical management frequently used in clinical trials to explore the effect of clinician time on the total cost of antidepressant therapy. Formal clinical management increased the cost of AD therapy to £283. This adjustment did not affect the total cost of combination therapy.

Combination therapy cost

The cost of a full course of CBT is £867 when provided by a suitably qualified and trained clinical psychologist. The cost of COMB therapy included the cost of the same AD therapy and standard care as outlined above and the cost of CBT. On average, the total cost of COMB therapy was £1,029.

Additional health service costs for the management of depression

It is well known that depressed people who are treated unsuccessfully or relapse continue to impose considerable extra costs for the healthcare sector as a consequence of their depression. Borghi and Guest (2000) estimated the expected cost of 5-month healthcare resource use attributable to managing a patient

suffering from moderate or severe depression who discontinues antidepressant treatment, to be £206 at 1997/98 prices. This estimate was inflated to 2002/03 prices and extrapolated to calculate the total cost of additional health service use over the 15-month period for people discontinuing initial treatment (£680), completing but not responding to treatment (£580), or relapsing during follow-up (£417).

Incremental cost-effectiveness of COMB versus AD therapy

In total, COMB therapy was estimated to be both more effective and more costly than AD treatment. On average, the strategy of COMB therapy was £637/£539 more costly per patient when not considering/considering the additional costs of intensive clinical management for antidepressant therapy. The resulting base case ICERs were £4,056/£3,431 per additional successfully treated patient and £6,286/£5,317 per QALY gained, respectively (***Table 3***).

Table 3. **Incremental cost and effectiveness of combination therapy versus antidepressant therapy for people with moderate/severe depression in secondary care**

	Number of additional successfully treated patients	Number of QALYs gained	Incremental cost per additional successfully treated patient	Incremental cost per QALY
COMB vs. AD with standard care	15	10	£4,056	£6,286
COMB vs. AD with intensive clinical management	15	10	£3,431	£5,317

Sensitivity analyses

One-way sensitivity analysis

The parameter values used in the sensitivity analyses and the relevant incremental cost-effectiveness ratios are listed in ***Table 4***. Overall the results indicated that the findings are relatively robust to the investigated parameters. The most significant component of uncertainty around the comparative cost-effectiveness of the two treatment strategies was the risk difference between AD and COMB therapy for no response when treatment is completed. All other factors played only minor roles in the variation of the estimate.

Table 4. **One-way sensitivity analysis (standard care scenario)**

Parameter	Range used in the sensitivity analysis (95% CI)	ICER (£/ additional successfully treated patient)	ICER (£/ QALY)
Clinical outcomes			
Risk difference in not completing treatment	0.00 - (-0.12)	4,654 – 3,588	7,804 – 5,249
Risk difference in no response when treatment is completed	(-0.08) – (-0.28)	6,129 – 2,984	10,022 – 4,503
Risk difference in relapse at 12-month follow-up	(-0.12) – (-0.24)	4,913 – 3,347	7,101 – 5,516
Health state utilities			
Severe depression, untreated	0.23 – 0.37	4,056	5,593 – 7,175
Fluoxetine treatment, no response	0.58 – 0.68	4,056	6,211 – 6,363
Fluoxetine treatment, response	0.76 – 0.84	4,056	6,378 – 6,196
Response, no treatment	0.82 – 0.90	4,056	6,681 – 5,935
Unit costs (all estimates are in prices £ 2002/03)			
Cost of depression management for patients discontinuing treatment over 5 months	£60 - £600	4,531 – 3,150	7,021 – 4,881

Probabilistic sensitivity analysis

To report the results of the probabilistic sensitivity analysis, cost-effectiveness acceptability curves were devised (***Figure 2 and 3***). The curves indicate the probability of COMB therapy being more cost-effective than the AD strategy for a range of potential threshold values. The threshold value is the maximum amount of money a decision maker would be willing to pay for a unit of effect, in this case for a successfully treated patient or a QALY.

The probabilistic analysis showed that if decision makers are not willing to pay more for additional benefit, COMB therapy is unlikely to be cost-effective. On the other hand, if decision makers are willing to pay £5,000 for an additional successfully treated patient with depression, the probability of COMB being cost-effective compared with AD therapy with clinical management or without clinical management is 68% or 78%. The likelihood of CBT being cost-effective would increase to 94% and 96% respectively if the decision maker's willingness to pay threshold for the same benefit is £10,000. The distance between the curves

for the two scenarios clearly illustrates that the results are also highly sensitive to the amount of clinical management patients receive during AD therapy. (***Figure 2***)

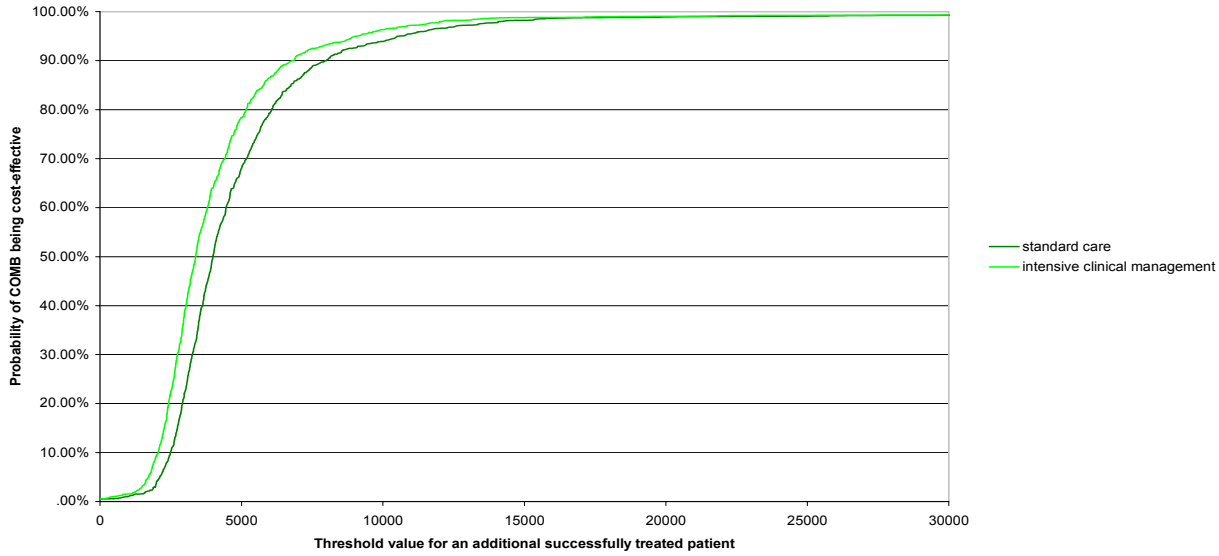

Figure 2. Cost-effectiveness acceptability curves of COMB therapy when compared with AD therapy for the treatment of moderate/severe depression in secondary care (benefits measured in terms of successfully treated patients)

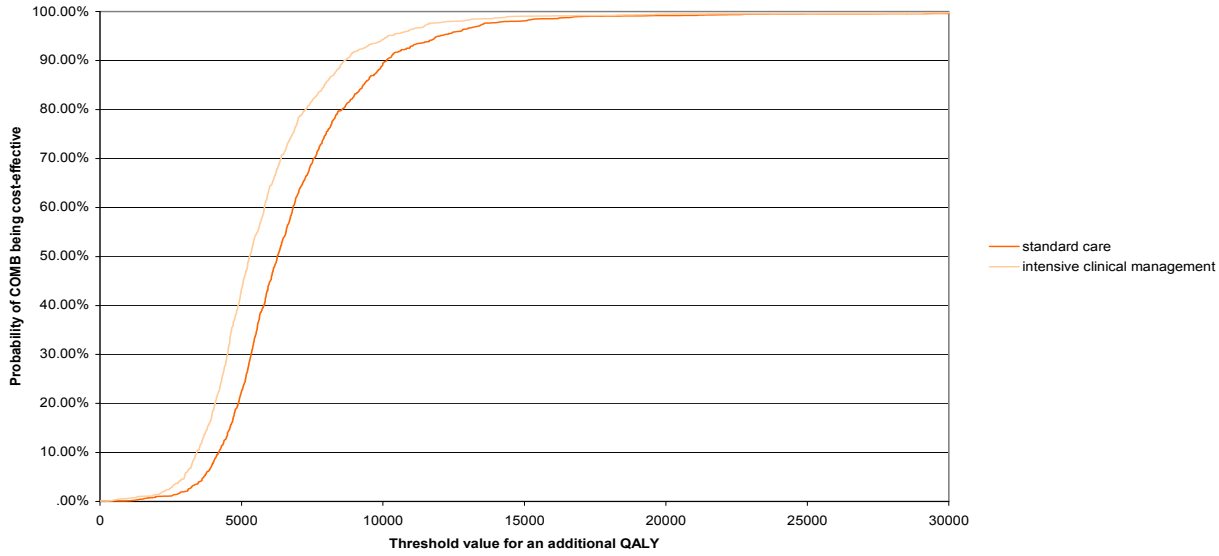

Figure 3. Cost-effectiveness acceptability curves of COMB therapy when compared with AD therapy for the treatment of moderate/severe depression in secondary care (benefits measured in terms of QALYs)

If we measure health benefits in terms of QALYs, the probability of COMB therapy being cost-effective slightly decreases, but still the curves demonstrate COMB therapy as a highly cost-effective strategy for the management of moderate/severe depression in secondary care. Furthermore, the likelihood of COMB therapy being cost-effective is above 90% if the threshold value is £10,000 or more. (***Figure 3***)

9.4.4 Discussion

The issue of the comparative cost-effectiveness of antidepressant therapy versus individual psychotherapy versus the combination of antidepressant therapy and individual psychotherapy for the management of people with moderate/severe depression in secondary care was identified as having a possible major cost impact on the NHS, but no existing cost-effectiveness evidence was available to facilitate the GDG's decision making process.

In the economic evaluation, CBT was chosen as the psychotherapy and fluoxetine as the antidepressant being compared. A cost-effectiveness model was constructed to investigate the difference in clinical outcomes and direct healthcare costs between the different strategies. Preliminary analyses showed that CBT alone is likely to be dominated by antidepressant therapy and therefore it was excluded from the final model. Combination therapy is both more effective and more costly than antidepressant therapy and these strategies were compared in a formal cost-effectiveness analysis.

The point estimate of the incremental cost per additional successfully treated patient varied between £4,056 and £3,431 depending on whether standard clinical support or intensive clinical management was provided with antidepressant therapy, and between £6,286 and £5,371 when benefits were measured in terms of QALYs gained. Uncertainty around these estimates was explored by sensitivity analyses, including a probabilistic analysis.

Based on the overall results, CBT alone is unlikely to be a cost-effective first-line therapy for patients with moderate/severe depression treated in secondary care. Combination therapy is likely to be a highly cost-effective treatment option for the same patient group.

It is anticipated that the type of antidepressant chosen for the model would not influence the relative cost-effectiveness of the two strategies significantly since the combination and antidepressant strategies include identical medication protocols. The same argument is likely to be valid for the cost of patients taking an overdose of antidepressants.

However, care should be taken that the wider provision of combination therapy might impose additional training needs for CBT and have considerable additional cost impact. This fact should be treated with caution when implementing the guideline locally. Due to the lack of sufficient clinical evidence, similar analysis could not be carried out using interpersonal psychotherapy (IPT) as the psychotherapy of choice.

Research recommendations

For future research, it is recommended that studies should:

- Explore the cost-effectiveness of the different newer antidepressants used as first-line treatments in the UK
- Determine the optimal length of maintenance antidepressant therapy
- Investigate the comparative cost-effectiveness of IPT versus CBT for the secondary care treatment of depression with regard to the non-disease specific nature and the lower training needs of IPT
- Measure the health-related quality-of-life of patients with depression in future studies
- Analyse the efficiency of improving the early detection of depression
- Estimate the overall cost impact of the implementation of the guideline.

10 References

ABPI. Edronax (reboxetine) SPC. Compendium of Data Sheets and Summaries of Product Characteristics. www.emc.vhn.net/professional/

The AGREE Collaboration. (2001). Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. *www.agreecollaboration.org* London: St George's Hospital Medical School

Akiskal, H.S. (1986) A developmental perspective on recurrent mood disorders: A review of studies in man. *Psychopharmacology Bulletin 22(3) 579-586*

Akiskal and McKinney, W.T. (1975) Overview of recent research in depression: integration of ten conceptual models into a comprehensive. *Archives of General Psychiatry,* 32, 285-305

Altshuler,L.L.; Bauer,M.; Frye,M.A.; Gitlin,M.J.; Mintz,J.; Szuba,M.P.; Leight,K.L.; Whybrow,P.C. (2001) Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 158(10):1617-22

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders. Fourth edition (DSM-IV).* Washington D.C.: APA

American Psychiatric Association (APA) (2000a) Handbook of psychiatric measures. Washington D.C.: APA.

American Psychiatric Association. (2000b). Practice guideline for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry, 157(suppl4)*, 1-45.

Anderson, I. M., & Edwards, J. G. (2001). Guidelines for choice of selective serotonin reuptake inhibitor in depressive illness. *Advances in Psychiatric Treatment, 7*, 170-180.

Anderson, I. M., Nutt, D. J., & Deakin, J. F. (2000). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology, 14*, 3-20.

Andrews G, & Jenkins R (1999). *Management of Mental Disorders* Volume 1. WHO Collaborating Centre for Mental Health and Substance Misuse (UK Edition).

Andrews,G. (2001) Placebo response in depression: bane of research, boon to therapy. *British Journal of Psychiatry*. 178:192-4.Angermeyer, M.C. & Matschinger, H. (1996) Public attitudes towards psychiatric treatment. *Acta Psychiatrica Scandinavica*, 94, 326-336.

Angst, J. (1993). Severity of depression and benzodiazepine co-medication in relationship to efficacy of antidepressants in acute trials: A meta-analysis of moclobemide trials. *Human Psychopharmacology, 8*, 401-408.

Araya R. Rojas G. Fritsch R. Gaete J. Rojas M. Simon G. Peters TJ. (2003) Treating depression in primary care in low-income women in Santiago, Chile: a randomised controlled trial. *Lancet*. 361(9362):995-1000

Aronson,R.; Offman,H.J.; Joffe,R.T.; Naylor,C.D. (1996) Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Archives of General Psychiatry* 53(9):842-8

Asberg, M., Montgomery, S., Perris, C, et al. (1978) A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavia 74,* 544-548.

Avery, D., & Winokur, G. (1976). Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. *Archives of General Psychiatry, 33,* 1029-1037.

Barbey, J. T., Roose, S. P. (1998). SSRI safety in overdose. *Journal of Clinical Psychiatry, 59(Suppl 15)*, 42-48.

Barbosa, L., Berk, M., Vorster, M. (2003) . A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *J Clin Psychiatry, 64(4)*, 403-7.

Barbui, C., & Hotopf, M. (2001). Amitriptyline v the rest: still the leading antidepressant after 40 years of randomised control trials. *British Journal of Psychiatry*, 178, 129-144.

Barbui,C., Hoptof,M., Freemantle,N.; Boynton,J., Churchill,R., Eccles,M.P., Geddes,J.R., Hardy,R., Lewis,G. & Mason,J.M. (2002) Treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs) (Cochrane Review). In: *The Cochrane Library, Issue 3*. Oxford: Software Update

Barkham, M., Rees, A., Stiles, W.B., Shapiro, M.A., Hardy, G.E. and Reynolds, S. 1996. Dose-effect relations in time-limited psychotherapy for depression . *Journal of Consulting and Clinical Psychology*, 64, 927-935

Barrett, J.E., Williams, J.W., Oxman, T.E., Katon, W., Frank, E., Hegel, M.T., Sullivan, M. and Schulberg, H.C. (1999). The treatment effectiveness project: A comparison of the effectiveness of paroxetine, problem-solving therapy, and placebo in the treatment of minor depression and dysthymia in primary care patients: Background and research. *Journal of Hospital Psychiatry*, 21, 260-273.

Bauer, M., Whybrow, P. C., Angst, J. Versiani, M. & Moller, H-J. (2002). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and Continuation Treatment of Major Depressive Disorder *The World Journal of Biological Psychiatry, 3* (1)5-43.

Bauer, M., Whybrow, P. C., Angst, J. Versiani, M. & Moller, H-J. (2002). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance Treatment of Major Depressive Disorder and Treatment of Chronic Depressive Disorders and Subthreshold Depressions *The World Journal of BiologicalPsychiatry, 3* (2) 69-86.

BDI website
http://www.criminology/unimelb.edu.au/victims/resources/assessment/affect/bdi.html
(10.05.02) (Version 1A)

Beck AT, Steer A, Brown G K. (1996) *Beck depression inventory manual, 2nd ed.* San Antonio: The Psychological Corporation.

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive Therapy of Depression*. New York: J. Wiley & Sons.

Beck, A.T. (2002) Personal communication to Paul Gilbert. 14.08.02

Beck, A.T., Beamesderfer, A. (1974) Assessment of depression: the depression inventory. In P. Pichot (ed.), *Modern problems in pharmacopsychiatry* (pp. 151-169). Basel, Switzerland: Karger.

Beck, A.T., Steer, R.A. (1987). *The Beck depression inventory manual*. San Antonio: The Psychological Corporation, Harcourt Brace Javanovich.

Beck, A.T., Steer, R.A., Garbin, M.G. (1988) 'Psychometric properties of the Beck Depression Inventory: 25 years of evaluation', *Clinical Psychology Review, 8, 77-100.* [version Ia]

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J. (1961) An inventory for measuring depression *Archives of General Psychiatry 4*, 561-571.

Beekman, A. F. T., Copeland, J. R. M., & Prince, M. J. (1999). Review of community prevalence of depression in later life. *British Journal of Psychiatry, 174*, 307-311.

Bennett, K.J., Torrance, G.W., Boyle, M.H., et al. (2000) Cost-utility analysis in depression: the McSad utility measure for depression health states. *Psychiatr Serv 2000*, 51:1171-1176

Berlin, J. A. (1997). Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group *Lancet, 350* (9072):185-6

Berto P, D'Ilario D, Ruffo P, et al. (2000) Depression: Cost-of-illness studies in the international literature, a review. *Journal of Mental Health Policy and Economics*, 3:3-10

Beutler, L. E., Clarkin, J. F & Bongar, B. (2000). *Guidelines for the Systematic Treatment of the Depressed Patient*. New York: Oxford University press.

Biddle, S. , Fox, K., Edmund, L. (1994). *Physical activity in primary care in England*. London: Health Education Authority.

Blashki TG, Mowbray R, Davies B. (1971) Controlled trial of amitriptyline in general practice. *British Medical Journal* 1(741):133-138.

Blatt, S. J., Zuroff, D. C., Quinlan, D. M., & Pilkonis, P. A. (1996a). Interpersonal factors in brief treatment of depression: Further analyses of the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Journal of Consulting & Clinical Psychology*, *64*, 162-171.

Blatt, S. J., Sanislow, C. A. III., Zuroff, D. C.;& Pilkonis, P. A. (1996b). Characteristics of effective therapists: Further analyses of data from the National Institute of Mental Health Treatment of antidepressants. *Journal of Consulting & Clinical Psychology.* 64(6):1276-84

Boardman AF (1987) The GHQ and the detection of mental health problems by physicians: a replicated study. *B J Psychiatry* 151, 373-381

Boeck (1982)

Bollini et al. (1999). Effectiveness of Antidepressants. *British Journal of Psychiatry, 174*, 297-393.

Borghi, J., Guest, J.F. (2000) Economic impact of using mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in the UK. *Eur Psychiatry, 15*:378-387

Bower, P., Byford, S., Sibbald, B., et al. (2000) Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy, and usual general practitioner care for patients with depression. II: Cost-effectiveness. *BMJ, 321*: 1389-1392

Bower, P., N., Rowland, & Hardy, R. (2003). The clinical effectiveness of counselling in primary care: A systematic review and meta-analysis. *Psychological Medicine*¸ 33, 203-215.

Bridges K, Goldberg DP (1985) Somatic presentations of DSM-3 psychiatric disorders in primary care. *J Psychosomatic Res.* 29, 563 - 569

Bridges K, Goldberg DP (1987) Somatic presentations of depressive illness in primary care. In The presentation of depression: Current approaches. Freeling,P., Downey,L., Malkin, J. (Eds) *Royal College of General Practitioners Occasional Paper No 36*

Briggs, A.H., Gray, A.M. (1999) Handling uncertainty when performing economic evaluation of healthcare interventions. *NICE Health Technology Assessment, 3*(2)

British Medical Association and the Royal Pharmaceutical Society of Great Britain. (2003) *British National Formulary (BNF)*, 45

Brown G & Harris T (1978). *The social origins of depression*. London: Tavistock

Brown, T., Campbell, L. A., Lehman, C. L., Grisham, J. R & Mancill, R. B. (2001). Current and life time comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology*, *110*, 585-599.

Buckley NA. Dawson AH. Whyte IM. Henry DA. (1994) Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet.* 343(8890) 159-162

Buckley NA. McManus PR. (2002) Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. *British Medical Journal*. 325(7376):1332-3

Bucknall, C., Brooks, D., Curry, P. V., Bridges, P. K., Bournas, N., & Ankier, S. I. (1988). Mianserin and trazodone for cardiac patients with depression. *European Journal of Clinical Pharmacology, 33(6),* 565-569.

Cahill, J., Barkharm, M., Hardy, G., Rees, A., Shapiro, D. A., Stiles, W. B., Macaskill, N. (2003). Outcomes of patients completing and not completing cognitive therapy for depression. *British Journal of Clinical Psychology*, *42*, 133-143.

Cameron E. (1947) The day hospital. An experimental form of hospitalization for psychiatric patients. *Modern Hospital* 69:60-3

Carcone, B., Vial, T., Chaillet, N., & Descotes, J. (1991). Symptomatic bradycardia caused by mianserin at therapeutic doses. *Hum Exp Toxicology, 10(5),* 383-384.

Carney, R. M., Freedland, K. E., Sheline, Y. I., Weiss, E. S. (1997). Depression and coronary heart disease: a review for cardiologists. *Clinical Cardiology, 70*, 196-200.

Casciano, J., Doyle, J., Arikian, S. (2001) The health economic impact of antidepressant usage from a payer's perspective: a multinational study. *IJCP, 55*:292-299

Cassano & Fava (2002) Depression and public health: an overiew. *J Psychosomatic Res.* 53, 849-857

Catalano, G., Catalano, M. C., Epstein, M. A., & Tsambiras, P. E. (2001). QTc interval prolongation associated with citalopram overdose: a case report and literature review. *Clinical Neuropharmacology, 24(3),* 158-162.

Chisholm D, Healey A, Knapp M. (1997) QALYs and mental health care. *Soc Psychiatry Psychiatr Epidemiol*; 32: 68-75

Chong, S. A., Mythily, Mahendran, R. (2001). Cardiac effects of psychotropic drugs. *Ann Acad Med Singapore, 30(6*), 625-631.

Christian, J. L., O'Leary, K. D., & Vivian, D. (1994). Depressive symptomatology in martially discordant women and men: The role of individual and relationship variables. *Journal of Family Psychiatry, 8*, 32-42.

Churchill, R., Hunot, V., Corney, R., Knapp, M. McGuire, H., Tylee, A., & Wessely, S. (2001). A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression. *Health Technology Assessment*, 5, 1-173.

Clinical Standards Advisory Group. (1999). *Services for Patients with Depression.* London: HMSO.

Cochrane Colloboration (2003) *Review Manager (RevMan) [Computer program]. Version 4.2 for Windows*. Oxford, England: The Cochrane Collaboration

Cohen J. (1988) *Statistical power analysis for the behavioural sciences.* Mahwah, NJ: Lawrence Erlbaum

Cohen, H. W., Gibson, G., Aldermann, M. H. (2000). Excess risk of myocardial infarction in patients treated with antidepressant medication: association with use of tricyclic agents. *American Journal of Medicine, 108*, 2-8.

Cole MG, Bellavance F, & Mansour A (1999) Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry* 156: 1182-1189

Committee on Safety of Medicines. (2000). Reminder: St John's Wort interactions. *Current Problems in Pharmacovigilance,* 26, 6-7.

Compufile Ltd. (1999) *Doctors' Independent Network database*. Surrey, England

Coryell W, Akiskal H, Leon AC et al (1994) The time course of untreated major depression; uniformity across episodes and samples. *Am J Psychiat 51*, 405-410

Cowen, P.J. (1998). Pharmacological management of treatment resistant depression. *Advances in Psychiatric Treatment, 4*, 320-327.

Cox AD, Pound A, Mills M, Puckering C, Owen AL. (1991) Evaluation of a home visiting and befriending scheme for young mothers: Newpin. *J R Soc Med* 84(4):217-20.

Creed F, Black D, Anthony P, Osborn M, Thomas P, Tomenson B. (1990) Randomised controlled trial of day patient versus inpatient psychiatric treatment. *BMJ* 300:1033-7

Cuijpers, P. (1997). Bibliotherapy in unipolar depression: a meta-analysis. *J Behav Ther & Exp Psychiat, 2,* 139-147.

Cullen, M., Mitchel, P., Broadaty, H., Boyce, P., Parker, G., Michie, I., & Wilhelm, K. (1991). Carbamazepine for treatment-resistant melancholia. *Journal of Clinical Psychiatry, 52*, 472-476.

Dago, P. L., & Quitkin, F. M. (1995). Role of the placebo response in the treatment of depressive disorders. *CNS Drugs, 4(5),* 335-340.

Davidson, J., & Pelton, S. (1986). Forms of atypical depression and their responses to antidepressant drugs. *Psychiatry Res,* 17, 87-95.

Davis, L. L., Kabel, D. Patel, D., Choate, A. D., Foslion-Nash, C., Guruis, G. N., Kramer, G. L., & Petty, F. (1996). Valproate as an antidepressant in major depressive disorder. *Psychopharmacoloy Bulletin, 32*, 647-652.

Davison GC. (2000) Stepped care: Doing More with Less? *J Con and Clin Psych* 68(4):580 -585.

Deeks JJ. (2002) Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Statistics in Medici*ne. 21(11):1575-600

Department of Health. (1996). C*linical guidelines: using clinical guidelines to improve patient care within the NHS*. Leeds: NHS Executive.

Department of Health, (1999). *The NHS Plan*. London: HMSO

Department of Health. (1999) National Service Framework for Mental Health. London: Department of Health.

Department Of Health (2001) *Treatment choice in psychological therapies and counselling evidence based clinical practice guideline*. London: Department of Health.

Department of Health (2002) Exercise referrals: a national quality assurance framework.

Department Of Health website: www.ppa.gov.uk and personal communication from the Prescription Pricing Authority to Carol Paton.

DerSimonian, R. & Laird, N. (1986). Meta-analysis in Clinical Trials. *Controlled Clinical Trials, 7,* 177-188.

DeRubeis, R. J., Gelfand, L.A., Tang, T.Z. & Simons, A. (1999). Medications versus cognitive behavior therapy for severely depressed outpatients: Mega-analysis of four randomized comparisons. *American Journal of Psychiatry, 156*, 1007-1013.

Dick P, Cameron L, Cohen D, Barlow, Ince A. (1985) Day and full time psychiatric treatment: a controlled comparison. *British Journal of Psychiatry* 147:246-9

Dietrich, D. E., & Emrich, H. M. (1998). The use of anticonvulsants to augment antidepressant medication. *Journal of Clinical Psychiatry, 59(Suppl 5),* 51-58.

Dohrenwend, B. P. (1990) 'The problem of validity in field studies of psychological disorders' revisited. *Psychological Medicine*, 20, 195-208.

Donald, R. C., Quitkin, F. M., & Klein, D. F. (2002). A typological model of estimation of drug and placebo effects in depression. *Journal of clinical psychopharmacology, 22*, 414-418.

Donoghue J, Tylee A. (1996a) The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. *Br J Psychiatry* 168(2):164-8.

Donoghue, J., Tylee, A., & Wildgust, H. (1996b). Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993-5. *British Medical Journal, 313*, 861-862.

Donoghue, J. & Hylan, T.R. (2001). Antidepressant use in clinical practice: efficacy v effectiveness. *British Journal of Psychiatry, 179 (suppl. 42)*, 9-17.

Donoghue, J. (2000). Antidepressant use patterns in clinical practices: comparisons among tricyclic antidepressants and selective serotonin reuptake inhibitors. *Acta Psychiatrica Scandinavica* , 101 (Suppl. 403), 57-61.

Donaghy M and Durwood B (2000) A report on the clinical effectiveness of physiotherapy in mental health. Chartered Society of Physiotherapy, London.

Doyle, J.J., Casciano, J., Arikian, S., et al. (2001) A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD). *Value in Health, 4(1)*:16-31

Drummond, M.F, Jefferson, T.O. on behalf of the BMJ Economic Evaluation Working Party. (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ, 313*: 275-283

Dunbar, G. C., Cohn, J. B., Fabre, L. F., Feighner, J. P., Fieve, R. R., Mendels, J., Shrivastava-RK AA, (1991) Imipramine -and-placebo-in-depressed-out-patients. A comparison of paroxetine, imipramine and placebo in depressed out-patients. *British Journal of Psychiatry;159*:394-398.

Dunn, R. L., Donoghue, J.M., & Ozminkowski, R. J. (1999). Longitudinal patterns of antidepressant prescribing in primary care in the UK: comparison with treatment guidelines. *Journal of Psychopharmacology, 13*, 136-143.

Eccles, M., Freemantle, N., & Mason, J. (1998). North of England evidence based guideline development project: Methods of developing guidelines for efficient drug use in primary care. *BMJ, 316,* 1232-1235.

Eccles M, Freemantle N, Mason J. (1999) North of England evidence-based guideline development project: summary version of guidelines for the choice of antidepressants for depression in primary care. *Family Practice*, 16(2):103-111.

Eccles M. Mason J. (2001) How to develop cost-conscious guidelines. *Health Technology Assessment (Winchester, England)*. 5(16):1-69

Edwards, J. G., & Goldie, A. (1983). Mianserin, maprotiline and intracardiac conduction. *British Journal of Clinical Pharmacology, 15 (Suppl.2),* 249S-254S.

Egan, G. (1990). *The Skilled Helper: A Systematic Approach to Effective Helping.* Pacific Grove: Brooks/Cole.

Egger, M., Davey Smith, G., Altman, D.G. (Eds.) (2001). *Systematic reviews in health care : meta-analysis in context.* London: BMJ.

Ehrenwald, J. (1976). *The History of Psychotherapy: From Healing Magic to Encounter*. New York: Jason Aronson.

Einarson, T. R., Arikian, S. R., Casciano, J., and Doyle, J. J., (1999). Comparison of extended-release venlafaxine, selective serotonin reuptake inhibitors, and tricyclic antidepressants in the treatment of depression: a meta-analysis of randomized controlled trials. *Clinical Therapeutics, 21*(2):296-308.

Elkin I, Shea MT, Watkins J, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, Fiester SJ, Parloff MB, (1989) 'National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments', *Archives of General Psychiatry*, 46, 971-982 [Version I]

Ellenberger, H .F. (1970). *The Discovery of the Unconscious. The History and Evolution of Dynamic Psychiatry*. New York: Basic Books.

Elliot,R. (Ed) (1998) Special Section: The Empirically Supported Treatments Controversy. *Psychotherapy Research* 8 (2) 115-170

Elliott, R. (1998). Editor's introduction: A guide to the empirically supported treatments controversy. *Psychotherapy Research*, 115-125.

Family Practice Notebook.com – http://www.fpnotebook.com/PSY74.htm (14/06/02) [version II]

Fava M & Kendler K (2000). Major depressive disorder. *Neuron*, 28: 335-341

Fava, M., Mulroy, R., Alpert, J. et al. (1997). Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *American Journal of Psychiatry, 154*,1760-1762.

Fawcett J. Epstein P. Fiester SJ. Elkin I. Autry JH. (1987) Clinical management--imipramine/placebo administration manual. NIMH Treatment of Depression Collaborative Research Program. *Psychopharmacology Bulletin*. 23(2):309-24

Feighner, J. P. (1995). Cardiovascular safety in depressed patients: focus on venlafaxine. *Journal of Clinical Psychiatry, 56(12),* 574-579.

Feighner, J.P., Boyer, W.F. (1989). Paroxetine in the treatment of depression: a comparison with imipramine and placebo. *Acta Psychiatrica Scandinavica, Supplementum, 350*, 125-129.

Feltham, C. & Horton, I. (Eds.) (2000). *Handbook of Counselling and Psychotherapy*. London: Sage.

Ferster, C. B. (1973). A functional analysis of depression. *American Psychologist*, 28, 857-870.

Fleishaker, J. C., Francom, S. F., Herman, B. D., Knuth, D. W., & Azie, N. E. (2001). Lack of effect of reboxetine on cardiac repolarization. *Clinical Pharmacological Therapy, 70(3)*, 261-269.

Fonagy P (2003). Some complexities in the relationship of psychoanalytic theory to technique. *Psychoanalytic Quarterly*, LXXII, 13-47

Ford, D. E., Mead, L. A., Chang, S. P., Cooper-Patrick, L., Wang, N. Y., King, M. I. (1998). Depression is a risk factor for coronary heart disease in men: a precursors study. *Archives of International Medicine*, 156, 1422-1426.

Forder, J., Kavanagh, S., Fenyo, A. (1996) A comparison of the cost-effectiveness of sertraline versus tricyclic antidepressants in primary care. *Journal of Affective Disorders, 38*:97-111

Fredman, S. J., Fava, M., Kienke, A. S. et al. (2000). Partial response, nonresponse and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current 'next-step' practices. *Journal of Clinical Psychiatry, 61*, 403-408.

Freeman, C.P.L., Power, M.J., Bowyer, D.J., Law, R.. (Unpublished) *Brief structured psychotherapies for neurotic disorders in primary care: a comparison of CBT, PT and treatment as usual at early and late intervention*

Freeman, H., Arikian, S., Lenox-Smith, A. (2000) Pharmacoeconomic analysis of antidepressants for major depressive disorder in the United Kingdom. *Pharmacoeconomics, 18(2)*: 143-148

Freemantle, N., House, A., Song, F., et al. (1994) Prescribing selective serotonin reuptake inhibitors as strategy for prevention of suicide. *BMJ, 309*: 249-253

Freemantle N, Mason J. (1995) Meta-analysis of antidepressant prescribing. *BMJ*, 311:751

Freemantle N, Mason J, Watt I. (1998) Evidence into practice. *Int J Techn Asses in Health Care,* 14(2): 387-391.

Freud, S (1917) Mourning and Melancholia. *Standard Edition of the Complete Psychological Works of Sigmund Freud.* Volume 14. London: Hogarth

Friedli, K., King, M.B., Lloyd, M. (2000) The economics of employing a counsellor in general practice: analysis of data from a randomised controlled trial. *British Journal of General Practice, 50*:276-283

Fulton, B., & Benfield, P. (1996). Moclobemide. An update of its pharmacological properties and therapeutic use. *Drugs, 52(6),* 869.

Furukawa TA, Kitamura T, Takahashi K (2000) Time to recovery from an inception cohort with hitherto untreated unipolar depressive episodes. *Brit J Psychiat* 177, 31-335

Furukawa, T. A., Streiner, D.L., & Young, L. T. (2002b). Antidepressant and benzodiazepine for major depression (Cochrane Review). In: *The Cochrane Library, Issue 4,* Oxford: Update Software.

Furukawa, T. A., McGuire, H., Barbui, C. (2002a). Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *BMJ*, 235 (7371): 991-999.

Gammell H, Ndahiro A, Nicholas M, Windsor J (1993) Refugees [political asylum seekers] Service provision and access to the NHS. A study by the College of Health for Newham Health Authority & Newham Healthcare.

Garnier, R. Azoyan, P., Chataigner, D., Taboulet, P., Dellattre, D., & Efthymiou, M. L. (1993). Acute fluvoxamine poisoning. *Journal Int Med Res*, 21(4), 197-208.

Gask, L., Goldberg, D., Lesser, A.L., Millar, T. (1998) Improving the psychiatric skills of the general practice trainee: an evaluation of a group training course. *Med Educ* 22,132-138

Geddes,J.R., Freemantle,N., Mason,J. Eccles,M.P. & Boynton,J. (2002) Selective serotonin reuptake inhibitors (SSRIs) for depression (Cochrane Review). In: *The Cochrane Library, Issue 1.* Oxford: Update Software

Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T.A., Kupfer, D. J., Frank, E., & Goodwin, G. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet, 361*, 653-661.

Gerber, P.D., Barrett, J.E., Barrett, J.A., Oxman, T.E., Manheimer, E., Smith, R., Whiting, R.D., (1992). The Relationship of presenting Physical Complaints to Depressive Symptoms in Primary Care Patients. *Journal of General Intern Medicine* 7(2):170-173.

Gilbert, P. (1992). *Depression: The Evolution of Powerlessness*. Hove: Psychology press.

Giles, D., Jarrett, R., Biggs, M., Guzick, D & Rush, J. (1989). Clinical predictors of reoccurrence in depression. *American Journal of Psychiatry,* 146, 764-767.

Gill B, Melzer H, Hinds K (1996) The prevalence of psychiatric morbidity among homeless adults Economic activity and social functioning of adults with psychiatric disorders. O*PCS Survey of Psychiatric morbidity Bulletin* 3. London, HMSO

Gitlin,M.J.; Weiner,H.; Fairbanks,L.; Hershman,J.M.; Friedfeld,N. (1987) Failure of T3 to potentiate tricyclic antidepressant response. *Journal ofAffective Disorders* 13(3):267-72

Glassman AH. Johnson LL. Giardina EG. Walsh BT. Roose SP. Cooper TB. Bigger JT Jr. (1983) The use of imipramine in depressed patients with congestive heart failure. *JAMA.* 250(15):1997-2001

Glassman, A. H., Roose, S. P., Bigger, J. T. Jr. (1993). The safety of tricyclic antidepressants in cardiac patients: risk benefit consideration. *Journal of the American Medical Association*, 9, 45-51.

Glassman, A. H., Shapiro, P. A. (1998). Depression and the course of coronary artery disease. *American Journal of Psychiatry, 155*, 4-11.

Glassman AH. O'Connor CM. Califf RM. Swedberg K. Schwartz P. Bigger Jr JT. Krishnan KRR. Van Zyl LT. Swenson JR. Finkel MS. Landau C. Shapiro PA. Pepine CJ. Mardekian J. Harrison WM. (2002) Sertraline treatment of major depression in patients with acute MI or unstable angina. J*ournal of the American Medical Association.* 288(6)701-709

Gloaguen V. Cottraux J. Cucherat M. Blackburn I-M. (1998) A meta-analysis of the effects of cognitive therapy in depressed patients. *Journal of Affective Disorders.* 49(1) 59-72

Goeringer, K. E., Raymond, L., Christian, G. D., & Logan, B. K. (2000). Postmortem forensic toxicology of selective serotonin reuptake inhibitors: a review of pharmacology and report of 168 cases. *Journal of Forensic Sci, 45(3),* 663-48.

Goh, K. T. (1996). Fatal overdose with citalopram*. Lancet, 347*,1345-1346.

Goldberg DP. Jenkins L. Millar T. Faragher EB. (1993) The ability of trainee general practitioners to identify psychological distress among their patients. Psychological Medicine. 23(1) 185-193

Goldberg DP, & Bridges K (1988a) Somatic presentations of psychiatric illness in primary care settings. *J Psychosomatic Research 32*, 137-144

Goldberg DP, Huxley PJ (1992) *Common mental disorders - a biosocial model.* London: Tavistock

Goldberg, D. and Huxley, P. (1980) *Mental Illness in the Community: Pathways to Psychiatric Care.* Tavistock:London

Goldberg DP, Jackson G, Gater R, Campbell M, Jennett N. (1996). The Treatment of Common Mental Disorders by a Community Team based in primary care: a cost effectiveness study. *Psychological Medicine 26*, 487-492

Goldberg DP, Steele J, Smith C, Spivey L (1980) Training family doctors to recognize psychiatric illness with increased accuracy. *Lancet 2*, 521-523

Goldberg DP, Williams P. (1988b) *The user's guide to the general health questionnaire.* Windsor: NFER-Nelson

Goldberg, D. & Gournay, K. (1997) *The General Practitioner, the Psychiatrist and the Burden of Mental Health Care.* London: Institute of Psychiatry.

Goldberg, D. P., Privett, M., Ustun, B. et al. (1998). The effects of detection and treatment on the outcome of major depression in primary care: A naturalistic study in 15 cities. *British Journal of General Practice, 48,* 1840-1844.

Goldfried, M.R., Castonguay, L.G., Hayes, A.M., Drozd, J.F., & Shapiro, D.A. (1997). A comparative analysis of the therapeutic process in Cognitive-Behavioural and Psychodynamic-Interpersonal Sessions. *Journal of Consulting and Clinical Psychology*, 65, 740-748.

Goodwin,G. (2000) Neurobiological aetiology of mood disorders. In Gelder,M.G., Lopez-Ibor,J.J. & Andreasen,N. (Eds). (2000) *New Oxford Textbook of Psychiatry* Chapter 4, 711-719

Gould RA, Clum GA. (1993). A meta-analysis of self-help treatment approaches. *Clin Psychol Rev, 13, 169-186.*

Grant C. Goodenough T. Harvey I. Hine C. (2000) A randomised controlled trial and economic evaluation of a referrals facilitator between primary care and the voluntary sector.*British Medical Journal.* 320(7232)419-423

Gray JA, Proudfoot J, Swain S 2000. 'Beating the Blues': computerised cognitive-behavioural therapy. *Journal of Primary Care Mental Health* 4, 17–18.

Greenberg, J.R., & Mitchell, S.A. (1983). *Object Relations in Psychoanalytic Theory*. Cambridge, Mass: Harvard University Press.

Greenberger, D. & Padesky, C. A. (1995). *Mind over Mood: A Cognitive Therapy Manual for Clients*. Guilford Press: New York.

Gregor, K. J. (1994). Selective serotonin reuptake inhibitor dose titration in the naturalistic setting. *Clinical Therapeutics, 16*, 306-315.

Greist, J., Mundt, J. C., & Kobak, K. (2002). Factors contributing to failed trials of antidepressants: can technology prevent some problems? *Journal of Clinical Psychiatry*, *63*, 8 – 13.Grundemar L., et al. (1997). Symptoms and signs of severe citalopram overdose. *Lancet*, 349:1602.

Guthrie, E., Moorey, J., Margison, F. (1999) Cost-effectiveness of brief psychodynamic-interpersonal therapy in high utilizers of psychiatric services. *Arc Gen Psychiatry, 56*:519-526

Guy, W. (1976) *Early Clinical Drug Evaluation Program Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76-338).* Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH

Haddad, P. M. (2001). Antidepressant discontinuation syndromes. *Drug Safety 24*,183-197.

Haefeli, W. E., Schoenenberger, R. A., & Scholer, A. (1991). Recurrent ventricular fibrillation in mianserin intoxication. *British Medical Journal, 16;302(6773*), 415-416.

Halbreich, U., Rojansky, N., Palter, S., Twoek, H., Hissin, P., & Wang, K. (1995). Estrogen augments serotonergic activity in postmenopausal women. *Biological Psychiatry, 37*, 434-441.

Hall, W. D., Mant, A., Mitchell, P. B., Randle, V. A., Hickie, I. B., & McMagnus, P. (2003). Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ, 326*, 1008-1011.

Hamilton, J. A., Grant, M., & Jensvold, M. F. (1996). *Sex and treatment of depression in psychopharmacology and women: Sex, gender and hormones.* Edited by M. J. Jensvold, U. Halbreich, & J. A. Hamilton. Washington DC: AHA Press, 241-260.

Hamilton, K. E., & Dobson, K. S. (2002). Cognitive therapy of depression: Pretreatment patient predictors of outcome. *Clinical Psychology Review*, 22, 875-893.

Hamilton, M. (1960) A rating scale for depression *J Neurol Neurosurg Psychiat 23,* 56-62.

Hammen C. Henry R. Daley SE. (2000) Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting & Clinical Psychology. 68(5):782-7*

Hardy, G.E., Cahill, J.C., Shapiro, D.A., Barkham, M., Rees, A. and Macaskill, N. 2001. Client, interpersonal and cognitive styles as predictors of response to time limited cognitive therapy for depression. *Journal of Consulting and Clinical*, 69, 841-845.

Harris EC. Barraclough B. (1997) Suicide as an outcome for mental disorders. A meta-analysis. *British Journal of Psychiatry.* 170:205-28

Harris, T., Brown, G. W., Robinson, R. (1999). Befriending as an intervention for chronic depression among women in an inner city. 1: Randomised controlled trial. *The British Journal of Psychiatry, 174*, 219-224.

Harris,T. Introduction to the work of George Brown. In Harris,T. (Ed). (2000). *Where Inner and Outer Worlds Meet. Psychosocial Research in the Tradition of George W. Brown.* London & New York: Routledge

Hatziandreu EJ, Brown RE, Revicki DA, et al. (1994) Cost utility of maintenance treatment of recurrent depression with sertraline versus episodic treatment with dothiepin. *Pharmacoeconomics*; 5(3): 249-264

Hawley, C. J., Gale, T. M. & Sivakumaran, T. (2002). How does the threshold score to enter a major depression trial influence the size of the available patient population for study? *Journal of Affective Disorders*, 71, 181-187.

Hayhurst, H., Cooper, Z., Paykel, E. S. et al. (1997). Expressed Emotion and Depression: A Longitudinal Study. *British Journal of Psychiatry, 171*, 439-443.

Healey, D. (2003). The emergence of antidepressant induced suicidality. *Primary Care Psychiatry, 6*, 23-28

Henry JA. Antao CA. (1992) Suicide and fatal antidepressant poisoning. *European Journal of Medicine.* 1(6) 343-8

Henry JA. (1993) Debits and credits in the management of depression. *Br J Psychiatry* 163(S20):33-39

Herran A, Vazquez-Barquero J, Dunn G (1999) Comment on Kessler et al; letter: *BMJ. 318:1558-9*

Herz MI, Endicott J, Spitzer RL, Mesnikoff A. (1971) Day versus inpatient hospitalization: a controlled study. *American Journal of Psychiatry* 10:1371-82

Hewer, W., Rost, W., & Gattaz, W. F. (1995). Cardiovascular effects of fluvoxamine and maprotiline in depressed patients. *Eur Arch Psychiatry Clin Neurosci, 246(1),* 1-6.

Hindmarsh, I., Kimber, S., Cockle, S. M. (2000). Abrupt and brief discontinuation of antidepressant treatment: effects on cognitive function and psychomotor performance. *International Clinical Psychopharmacology, 15*, 305-318.

Hippisley-Cox, J., Pringle, M., Hammersley, V., Crown, N., Wynn, A., Meal, A., Coupland, C. (2001). Antidepressants as a risk factor for ischaemic heart disease: case-control study in primary care. *British Medical Journal,* 323**,** 666-9.

Higgins JPT. Thompson SG. (2002) Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 21(11) 1539-1558

Hla, K. K., & Boyd, O. (1987). Mianserin and complete heart block. *Human Toxixology, 6(5)*, 401-402.

Hollon, S. D., Thase, M. E. & Markowitz, J. C. (2002). Treatment and prevention of depression. *Psychological Science 3 (suppletment 2) 39 – 77.*

Holm, K. J. , & Spencer, C. M. (1999). Reboxetine: a review of its use in depression. *CNS Drugs, 12*, 65-83.

Holmes, J. (2001). *The Search for a Secure Base: Attachment Theory and Psychotherapy*. Brunner-Routledge: London.

Hopko, D.R., Lejuez, C.W., Ruggiero, K.J. and Eifert, G.H. (2003). Contemporary behavioural activation treatments for depression: Procedures, principles, and progress. *Clinical Psychology Review,* 23, 699-717.

Hooley, T. M., & Teasdale, J. D. (1989). Predictors of relapse in unipolar depressives: Expressed emotion, marital distress and perceived criticism. *Journal of Abnormal Psychology*, 98, 229-235.

Hoult J, Reynolds I, Charbonneau Powis M, Weekes P, Briggs J. (1983) Psychiatric hospital versus community treatment: the results of a randomised trial. *Australian and New Zealand Journal of Psychiatry 17:160-7*

HRSD website – http://www.rag.org.au/drbill/depresstest.htm (01/07/02)

Hughes D. Morris S. McGuire A. (1997) The cost of depression in the elderly. Effects of drug therapy. *Drugs & Aging. 10(1):59-68*

Hunkeler EM, Meresman JF, Hargreaves WA, Fireman B, Berman WH, Kirsch AJ, Groebe J, Hurt SW, Braden P, Getzell M, Feigenbaum PA, Peng T, Salzer M. (2000) Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Archives of Family Medicine 9:700-708.*

Hurley, S. C. (2002). Lamotrigine update and its use in mood disorders. *Annals of Pharmacotherapy, 36*, 860-873.

Iliffe S. Haines A. Gallivan S. Booroff A. Goldenberg E. Morgan P. (1991) Assessment of elderly people in general practice. 1. Social circumstances and mental state. *British Journal of General Practice. 41(342) 9-12*

Institute of Medicine (2001) *Neurologic, psychiatric and developmental disorders.* Washington: Institute of Medicine

Isacsson G. Holmgren P. Druid H. Bergman U. (1997) The utilization of antidepressants-a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992-1994. *Acta Psychiatrica Scandinavica.* 96(2):94-100

Isacsson, G., Boethius, G., Henriksson, S. et al. (1999). Selective serotonin reuptake inhibitors have broadened the utilisation of antidepressant treatment in accordance with recommendations: findings from a Swedish prescription database. *Journal of Affective Disorders, 53*, 15-22.

Isbister, G. K., Prior, F. H., Foy, A. (2001). Citalopram-induced bradycardia and presyncope. *Ann Pharmacotherapy, 35(12),* 1552-1555.

Jackson, S.W. (1986). *Melancholia & Depression: From Hippocratic Times to Modern Times*. New Haven: Yale University Press.

Jackson, W. K., Roose, S. P., & Glassman, A. H. (1987). Cardiovascular toxicity of antidepressant medications. *Psychopathology, 20(Suppl.1*), 64-74.

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., Gortner, E., & Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of Consulting & Clinical Psychology*, 64, 295-304.

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials, 17 (1),* 1-12.

Janowsky, D. , Curtis, G., Zisook, S., Kuhn, K., Resovsky, K., & LeWinter, M. (1983). Trazodone-aggrevated ventricular arrhythmias. *Journal of Clinical Psychopharmacology, 3(6)*, 372-376.

Jarrett RB, Schaffer M, McIntire D, Witt-Browder A, Kraft D, Risser RC. (1999) Treatment of atypical depression with cognitive therapy or phenelzine: a double-blind, placebo-controlled trial. *Archives of General Psychiatry* 56(5):431-437

Jenkins R, Lewis G, Bebbington P et al (2003) The National Psychiatric Morbidity Survey of Great Britain – initial findings from the household survey. *International Review of Psychiatry 15, 29-42*

Joffe,R.T.; Singer,W. (1990) A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Research* 32(3):241-51

Johnson, J., Howarth, E., & Weissman, M. M. (1991). The validity of major depression with psychotic features based on a community sample. *Arch Gen Psychiatry, 48*, 1075-1081.

Johnstone A, Goldberg DP (1976) Psychiatric screening in general practice: a controlled trial. *Lancet I, 605-608*

Jones, E. & Asen, E. (1999). *Systemic Couple Therapy and Depression*. London: Karnac.

Jonsson B, Bebbington P. (1993) Economic studies of the treatment of depressive illness. In: Jonsson B & Rosenbaum J (eds) *Health economics of depression*. John Wiley & Sons, Chichester

Jonsson, B., Bebbington, P.E. (1994) What price depression? The cost of depression and the cost-effectiveness of pharmacological treatment. *British Journal of Psychiatry, 164*:665-673

Jorm, A. F., Christensen, H., Griffiths, K. M., Rodgers, B. (2002). Effectiveness of complementary and self-help treatments for depression. *MJA, 176, S84-S96.*

Joy CB, Adams CE, Rice K. (2003) Crisis intervention for people with severe mental illnesses (Cochrane Review). In: *The Cochrane Library, Issue 3*. Oxford: Update Software.

Kahn, E. (1985). Heinz Kohut and Carl Rogers: A timely comparison. *American Psychologist, 40*, 893-904.

Kaltenthalter, E., Shackley, P., Stevens, K. (2002) A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety. *HTA, 6*(22)

Karasu TB. (1986) The specificity versus nonspecificity dilemma: toward identifying therapeutic change agents. *American Journal of Psychiatry.* 143(6):687-95

Karasu, T. B. (1990). Toward a clinical model of the psychotherapy for depression, II: An integrative and selective treatment approach. *American Journal of Psychiatry*, 147, 269-278.

Katon W, Robinson P, Von Korff M, Lin E, Bush T, Ludman E, Simon G, Walker E. (1996) A multifaceted intervention to improve treatment of depression in primary care. *Archives of General Psychiatry 53(10):924-932.*

Katon W, Von Korff M, Lin E, Bush T, Ormel J. (1992) Adequacy and duration of antidepressant treatment in primary care. *Med Care 30:67-76.*

Katon W, Von Korff M, Lin E, Walker E, Simon GE, Bush T, Robinson P, Russo J. (1995) Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *JAMA 273(13):1026-1031.*

Katzelnick DJ, Simon GE, Pearson SD, Manning WG, Helstad CP, Henk HJ, Cole SM, Lin EH, Taylor LH, Kobak KA. (2000) Randomized trial of a depression management program in high utilizers of medical care. *Archives of Family Medicine 9(4):345-351.*

Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J (2000) 'A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression', *New England Journal of Medicine*, 340 (20), 1462-1470.

Keller, M. B., Lavori, P. W., Rice, J., Coryell, W. Hirschfeld, R. M. (1986). The persistent risk of chronicity in recurrent episodes of non-polar major depressive disorder: a prospective follow up. *American Journal of Psychiatry, 142*, 24-8.

Kendall, P.C., Hollon, S.D., Beck, A.T., Hammen, C.L., Ingram, R.E. (1987) 'Issues and recommendations regarding use of the Beck Depression Inventory', *Cognitive Therapy and Research, 11(3), 289-299.* [Version I]

Kendler L & Prescott C (1999). A population based twin study of lifetime major depression in men and women. *Archives of General Psychiatry*, 56: 39-44

Kendler KS. Gardner CO. Neale MC. Prescott CA. (2001) Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychological Medicine. 31(4):605-16*

Kendrick T, Stevens L, Bryant A, Goddard J, Stevens A, Raftery J, Thompson C. (2001) Hampshire depression project: changes in the process of care and cost consequences. *Br J Gen Pract. 51: 911-913.*

Kessler D. Lloyd K. Lewis G. Gray DP. (1999) Cross sectional study of symptom attribution and recognition of depression and anxiety in primary care. *Brit Med. J. 318, 436 - 43*

Kessler RC, McGonagle KA, Zhao S et al (1994) Lifetime and 12 month prevalence of DSM3-R psychiatric disorders in the United States. *Archives of General Psychiatry, 51*, 8-19

Ketter, T. A., Post, R. M., Parekh, P. I., Worthington, K. (1995). Addition of mono-amine oxidase inhibitors to carbamazepine: preliminary evidence of safety and antidepressant efficacy in treatment resistant depression. *Journal of Psychiatry, 56*, 471-475.

Khan, A., Dager, S. R., Cohen, S., Avery, D. H., Scherzo, B., & Dunner, D. L. (1991). Chronicity of depressive episode in relation to antidepressant – placebo response. *Neuropsychopharmacology, 4 (2),* 125-130.

Khan, A., Khan, S., Kolts, R. et al .(2003). Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo:analysis of FDA reports.*Am Journal of Psychiatry 160*,790-792.

Khan, A., Leventhal, R., Khan, S., & Brown, W. (2002). Severity of depression and response to Antidepressants and placebo: An analysis of the FDA database. *Journal of Clinical Psychopharmacology, 22*, 40-45.

Khan, A., Warner, H. A., & Brown, W. A. (2000). Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. *Archives of General Psychiatry, 57*, 311-317.

Kind and Sorensen (1993) The costs of depression. *Int. Clin. Psychopharmacol* 7, 191-195

Kind, P., Sorensen, J. (1995) Modelling the cost-effectiveness of the prophylactic use of SSRIs in the treatment of depression. *Int Clin Psychopharmacology, 10*(Suppl 1): 41-48

King, M., Sibbald, B., Ward, E., et al. (2000) Randomised controlled trial of non-directive counselling , cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care. *HTA, 4*(19)

Kirsch, I.; Scoboria, A. (2001) Apples, oranges, and placebos: Heterogeneity in a meta-analysis of placebo effects. *Advances in Mind-Body Medicine* 17(4) 307-309

Kirsch, I, Moore, T. M., Scoboria, A., & Nicholls, S. S. (2002). The Emperor's new drugs: an analysis of antidepressant medication data submittd to the U.S. Food and Drug Administration. *Prevention and Treatment, 5*, Article 23.

Kirsch, I; Scoboria, A; Moore, T J.(2002) Antidepressants and placebos: Secrets, revelations, and unanswered questions. *Prevention & Treatment, 5, Article 33.*

Kirsch, I. (2000). Are drug and placebo effects in depression additive? *Biological Psychiatry, 47*, 733-735.

Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: a meta-analysis of antidepressant medication. *Prevention and Treatment, 1*, Article 0002a.

Kisely S, Gater, R, Goldberg DP (1995) Results from the Manchester Centre in Ustun,T.B. & Sartorius,N. (Eds).(1995) *Mental illness in General Health Care: An international study.* Chichester: Wiley. Pp175- 191

Klerman, G. L., Weissman, M. M., Rounsaville, R. J.& Chevron, E. S. (1984) *Interpersonal Psychotherapy of Depression*. New York: Basic Books.

Kornstein SG. Schatzberg AF. Thase ME. Yonkers KA. McCullough JP. Keitner GI. Gelenberg AJ. Davis SM. Harrison WM. Keller MB. (2000) Gender differences in treatment response to sertraline versus imipramine in chronic depression. *American Journal of Psychiatry. 157(9) 1445-1452*

Knapp M. Ilson S. (2002) Economic aspects of depression and its treatment. *Current Opinion in Psychiatry 15(1) 69-75*

Kornstein, S. G. (1997). Gender differences in depression: Implications for treatment. *Journal of Clinical Psychiatry, 58 (Suppl 15),* 12-18.

Kramer, J.C., Klein, D.F., & Fink, M. (1961). Withdrawal symptoms following discontinuation of imipramine therapy. *American Journal of Psychiatry, 118*, 549-550.

Kris EB. (1965) Day hospitals. *Current Therapeutic Research* 7:320-3

Kuhn R. (1958) The treatment of depressive states with G 22355 (imipramine hydrochloride). *American Journal of Psychiatry* 115: 459–64

Kupfer DJ (1991). Long-term treatment of depression. J Clin Psychiatry, 52:28-34 (suppl).

Lancaster, S. G., & Gonzalez, J. P. (1989). Lofepramine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness.*Drugs,37(2)*123-140.

Lebowitz, B. D., Pearson, J.L., Schneider, L.S. et al. (1997). Diagnosis and treatment of depression in later life. *JAMA, 278*, 1186-1190.

Lee, A. S., Murray, R. M. (1988). The long term outcome of Maudsley depressives. *British Journal of Psychiatry, 153*, 741-751.

Leff, J., Vearnals, S., Brewin, C.R., et al. (2000) The London Depression Intervention Trial. *British Journal of Psychiatry, 177*:95-100

Leichsenring, F. (2001). Comparative effects of short-term psychodynamic psychotherapy and cognitive-behavioral therapy in Depression: A meta-analytic approach. *Clinical Psychology Review, 21*, 401-419.

Leith, L. M. (1994). *Foundations of exercise and mental health*. Morgantown, WV: Fitness Information Technology, 17-44.

Lejoyeux, M. & Ades, J. (1997). Antidepressant discontinuation: a review of the literature. *J Clin Psychiatry, 58 (Suppl. 7), 11-15.*

Lejoyeux, M., Ades, J., Mourad, I. (1996). Antidepressant withdrawal syndrome: recognition, prevention and management. *CNS Drugs, 5*, 278-292.

Lepine, J.P., Gastpar, M., Mendlewicz, J. et al. (1997). Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). *International Clinical Psychopharmacology, 12, 19-29.*

Lepore, S. J. (1997). Expressive writing moderates the relation between intrusive thoughts and depressive symptoms. *Journal of Personality and Social Psychology, 73, 1030-1037.*

Lesperance F, Frasure-Smith N. (2000). Depression in service users with cardiac disease: a practical review. *J Psychosom Res* April-May, 48, 4-5

Lewis, G., Anderson, L., Araya, R., Elgie, R., Harrison, G, Proudfoot, J, Schmidt, U, Sharp, D, Williams C. Self-Help Interventions for Mental Health Problems. *Commissioned DoH report:* London.

Lewis G. Hawton K. Jones P. (1997) Strategies for preventing suicide. *British Journal of Psychiatry*. 171:351-4

Lewinsohn, P.M. (1975). The behavioral study and treatment of depression. In M. Hersen, R.M. Eisler, & P.M. Miller (Eds.*), Progress in Behavior Modification, Vol. 1.* New York: Academic Press.

Lexchin, J., Bero, L.A., Djulbegovic, B., and Clark, O. (2003). Pharmaceutical industry sponsorship and research outcome and quality: systematic review *BMJ*; 326: 1167 - 1170.

Linde, K., & Mulrow, C. D. (2003). St John's wort for depression. *Cochrane Database of Systematic Reviews, 3.* Cochrane Depression, Anxiety and Neurosis Group

Livingstone, M. G., & Livingstone, H. M. (1996). Monoamine oxidase inhibitors: an update on drug interactions. *Drug safety, 14*, 219-227.

Loosen, P.T. (1987) The TRH stimulation test in psychiatric disorders: A review. In Nemeroff, C.B.& Loosen, P.T. (Eds). (1987). *Handbook of clinical psychoneuroendocrinology* 336-360

Londborg, P. D. (1999). Lamotrigine in the treatment of unipolar depression. *Abstract at 152nd Annual Meeting of the American Psychiatric Association, Washington DC.*

Lovell, K. & Richards, D. Multiple access points and levels of entry (MAPLE): ensuring choice, accessibility and equity for CBT services. *Behavioural and Cognitive Psychotherapy 2000; 28:379-392.*

MacDonald, T. M., McMahon, A.D., Reid, I.C. et al. (1996). Antidepressant drug use in primary care: a record linkage study in Tayside, Scotland. *British Medical Journal, 313*, 860-861.

MADRS website: http://195.101.204.50:443/public/MADRS.html (21/01/03)

Maes M. Meltzer HY. Cosyns P. Suy E. Schotte C. (1993) An evaluation of basal hypothalamic-pituitary-thyroid axis function in depression: results of a large-scaled and controlled study. *Psychoneuroendocrinology*. 18(8):607-20

Malt, U.F., Herman Robak, O., Madsbu, H-P., Bakke, O., & Loeb, M. (1999). The Norwegian naturalistic treatment study of depression in general practice (NORDEP) – I: randomised double blind study. *BMJ*, 318, 1180-1184.

Markowitz, J. C., DeVane, C. L., Liston, H. L. et al. (2000). An assessment of selective serotonin reuptake inhibitor discontinuation symptoms with citalopram. *International Clinical Psychopharmacology, 15*, 329-333.

Marks J, Goldberg D, Hillier V (1979) Determinants of the ability of general practitioners to detect psychological illness. *Psychological Medicine 9*, 337-353

Marks IM. Mataix-Cols D. Kenwright M. Cameron R. Hirsch S. Gega L. (2003) Pragmatic evaluation of computer-aided self-help for anxiety and depression. *British Journal of Psychiatry.* 183:57-65

Marshall M. Crowther R. Almaraz-Serrano A. Creed F. Sledge W. Kluiter H. Roberts C. Hill E. Wiersma D. Bond GR. Huxley P. Tyrer P. (2001) Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care. *Health Technology Assessment* (Winchester, England). 5(21) i-iii+1-65)

Marshall M, Crowther R, Almaraz-Serrano AM, Tyrer P. (2003) Day hospital versus out-patient care for psychiatric disorders (Cochrane Review). In: *The Cochrane Library*, Issue 3. Oxford: Update Software

McCrone, P., Knapp, M., Proudfoot, J. et al. (2003) *Cost-effectiveness of computerised cognitive behavioural therapy for anxiety and depression in primary care*. (work in progress)

McCullough, J.P. Jr. (2000). *Treatment for Chronic Depression: Cognitive Behavioral Analysis System of Psychotherapy*. New York: Guildford.

McGrath, P. J., Blood, D. K., Stewart, J. W., Harrison, W., Quitkin, F. M., Tricamo, E., & Markowitz, J. (1987a). A comparative study of the electrocardiographic effects of phenelzine, tricyclic antidepressants, mianserin, and placebo. *Journal of Clinical Psychopharmacology, 7(5),* 335-339.

McGrath, P. J., Stewart, J. W., Harrison, W., & Quitkin, F. M. (1987b). Treatment of refractory depression with monoamine oxidase inhibitor antidepressant. *Psychopharmacology Bulletin, 23*, 169-72.

McGrath, P. J., Stewart, J. W., Nunes, E. V. et al. (1993). A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment refractory depression. *American Journal of Psychiatry, 150*, 118-123.

Meier, C. R., Schlienger, R. G., & Jick, H. (2001). Use of selective serotonin reuptake inhibitors and risk or developing first time myocardial infarction. *British Journal of Clinical Pharmacology, 57*, 179-184.

Meijer, W. E. E., Bouvy, M. L., Heerdink, E. R. (2001). Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. *British Journal of Psychiatry, 179*, 519-522.

Melander, H., Ahlqvist-Rastad, J., Meijer, G., & Beerman, B. (2003). Evidence based medicine selective reporting from studies sponsored by the pharmaceutical industry: review of studies in new drug applications. *British Medical Journal 326*, 1171 – 1173.

Meltzer H, Gill B, Petticrew M, Hinds K (1995b) Economic activity and social functioning of adults with psychiatric disorders. *OPCS Survey of Psychiatric morbidity Report 3*. London: HMSO

Meltzer H, Gill B, Petticrew M, Hinds K (1995a) The prevalence of psychiatric morbidity among adults living in private households. *OPCS Survey of Psychiatric morbidity Report 1.* London: HMSO

Meltzer H. Bebbington P. Brugha T. Farrell M. Jenkins R. Lewis G. The reluctance to seek treatment for neurotic disorders. *Journal of Mental Health.* Vol 9(3) (pp 319-327), 2000

Merriman, S. H. (1999). Monoamine oxidase drugs and diet. *Journal of Human Nutrition and Dietetics, 12*, 21-28.

Michelson, D., Fava, M., Amsterdam, J. et al. (2000). Interruption of selective serotonin reuptake inhibitor treatment. *British Journal of Psychiatry, 176*, 363-368.

Miller, P., Chilvers, C., Dewey, M. et al. (2003) Counselling versus antidepressant therapy for the treatment of mild to moderate depression in primary care. *Int J Tech Ass in Health Care, 19(1)*: 80-90

Mills, M., & Pound, A. (1996) Mechanisms of change: The Newpin Project, *Mrace Bulletin, vol. 2*, pp. 3—7.

Mindham,R.H. (1982) Tricyclic antidepressants. In Tyrer,P. (Ed) (1982) *Drugs in Psychiatric Practice.* Cambridge: Cambridge University Press

Mitchell, P. B. (1997). Drug interactions of clinical significance with selective serotonin reuptake inhibitors. *Drug Safety, 17,* 390-406.

Moncrieff. J., Wessely, S., & Hardy, R. (2001). Active placebos versus antidepressants for depression. *The Cochrane Library*, Volume (Issue 4).

Montgomery, S.A., Asberg, M. (1979) A new depression scale designed to be sensitive to change *British Journal of Psychiatry, 134*, 382-389.

Montgomery SA, Brown RE, Clark M. (1996) Economic analysis of treating depression with nefazodone v. imipramine. *British Journal of Psychiatry*; 168: 768-771

Mucci, M. (1997). *Reboxetine: a review of antidepressant tolerability*. London: Martin Dunitz.

Murray,C.J.L., Lopez,A.D., Jamison,D.T. (1994) The global burden of disease in 1990: Summary results, sensitivity analysis and future directions. *Bulletin of the World Health Organization, 72(3) 495-509*

Murray, C. J., & Lopez, A. D. (1997). Global morality, disability, and the contribution of risk factors: Global burden of disease study. *Lancet, 349*, 1436-1442.

Musselman, D. L., Evans, D. L., Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease. *Archives of General Psyhiatry, 55*, 580-592.

Mynors-Wallis, L. M., Gath, D. H., Baker, F. (2000). Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. *BMJ,* 320, 26-30.

Mynors-Wallis, L., Davies, I., Gray, A. (1997) A randomised controlled trial and cost analysis of problem-solving treatment for emotional disorders given by community nurses in primary care. *British Journal of Psychiatry, 170*:113-119

National Center for Alternative and Complementary Medicine (NCCAM). (Revised Aug 2002). *St. John's Wort and the treatment of depression.* NCCAM Publication No. D005. Retrieved 6 August, 2003, from http://nccam.nih.gov/health/stjohnswort/index.htm

National Depression Campaign (1999) *National Depression Campaign Survey*

National Institute for Clinical Excellence (NICE) (2001). *The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups.* London: National Institute for Clinical Excellence.

National Institute for Clinical Excellence (NICE) (2002). *Technology Appraisal No. 51. Guidance on the use of computerised cognitive behavioural therapy for anxiety and depression.* London: National Institute for Clinical Excellence.

National Institute for Clinical Excellence (NICE) (2003). *Technology Appraisal No. 59. Guidance on the use of electroconvulsive therapy.* London: National Institute for Clinical Excellence.

National Screening Committee, Health Departments of the United Kingdom. (1998) *First Report of the NSC.* Yorkshire: Department of Health

Netten, A., Rees, T., Harrison, G. (2002) *Unit costs of health and social care.* Personal Social Services Research Unit, Canterbury

Nezu, A. M., Nezu, C. M., & Perri, M. G. (1989). *Problem-solving therapy for depression: Theory research and clinical guidelines.* New York: Wiley.

Nezu, A.M. (1987). A problem-solving formulation of depression: A literature review and proposal of a pluralistic model. *Clinical Psychology Review*, 7, 121-144.

Nirenberg, A. A., & Amsterdam, J. J. (1990). Treatment resistant depression: definition and treatment approaches. *Journal of Clinical Psychiatry, 51*, 39-47.

Nolen, W. A., Hoencampe, E., Halmans, P. M. J. (1994). Classical and selective monoamine oxidase inhibitors in refractory major depression. In W. A. Nolen, S. P. Zohar, S. P. Roose, & J. D. Amsterdam (Eds.), *Refractory Depression: Current Strategies and Future Directions* (pp59-68). Chichester: John Wiley .

Nolen WA, van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, Haffmans J (1988) Treatment strategy in depression. II. MAO inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatrica Scandinavica*. 78(6):676-83

Norcorss, J.C. (Ed.)(2002). *Psychotherapy Relationships that Work: Therapist Contributions and Responsiveness to Patients*. New York: Oxford University Press.

Norcross, J. C., & Goldfried, M. R. (1992). *Handbook of Psychotherapy Integration*. New York: Basic Books.

Normann, C., Hummel, B., Scharer, L. O., Horn, M., Grunze, H, & Walden, J. (2002). Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled study. *Journal of Clinical Psychiatry, 63*, 337-344.

Nuechterlein KH & Dawson ME (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin*, 10, 300-312

Nutt, D. J. (2002).Tolerability and safety aspects of mirtazapine. *Human Psychopharmacology, 17(Suppl. 1)*, S37-41.

Office of National Statistics (2000) *Key health statistics from general practice 1998*. London: National Statistics

Ormel J. Van den Brink W. Koeter MWJ. Giel R. Van der Meer K. Van de Willige G. Wilmink FW. (1990) Recognition, management and outcome of psychological disorders in primary care: A naturalistic follow-up study. *Psychological Medicine*. 20(4) 909-923

Ormel J, Costa e Silva JA.(1995) The impact of psychopathology on disability and health perceptions. In: Üstün ,T.B. and Sartorius,N. (Eds) (1995) *Mental illness in general health care. An international study* pp.335-346. Chichester: J.Wiley & Sons

Ormel J, VonKorff M, Brink W.van den, Katon W, Brilman E, Oldehinkel T. (1993) Depression, anxiety, and social disability show synchrony of change in primary care patients. *Am J Public Health, 83*, 385-390.

Ormel J, Vonkorff M, Oldehinkel T, Simon G, Tiemens B, Ustun TB (1999) Onset of disability in depressed and non-depressed primary care patients. *Psychol Med. 29*, 847 -853

Osgood-Hynes DJ, Greist DH, Marks IM, Baer L, Heneman SW, Wenzel KW, Manzo PA, Parkin JR, Spierings CJ, Dottl SL, Vitse JM. (1998). Self-administered psychotherapy for depression using a telephone-accessed computer system plus booklets: an open US-UK study. *Journal of Clinical Psychiatry, 59*, 358-365.

Ostler K, Thompson C, Peveler RC, Kinmonth AL., Stevens R & A (2001) Influence of socio-economic deprivation on the prevalence and outcome of depression. *Br J Psychiatry.178*:12 - 17

Ostroff & Nelson. (1999). Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J.Clin.Psychiat, 60*, 256-259.

Ostrom (1996)

Palmer, S. C., Coyne, J.C. (2003). Screening for depression in medical care. Pitfalls, alternatives, and revised priorities. *Journal of Psychosomatic Research, 54*, 279-287.

Peet, M. & Pratt, J.P. (1993). Lithium. Current status in psychiatric disorder. *Drugs, 46*, 7-17.

Peet, M. Tienari, P., & Jaskari, M. O. (1977). A comparison of the cardiac effects of mianserin and amitriptyline in men. *Pharmakopsychiatr Neuropsychopharmakol, 10(6),* 309-312.

Pennix BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, Van Eijk JT, Van Tilburg W. (2001) Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 58(3): 221-7

Penttinen, J., & Valonen, P. (1996). Use of psychotropic drugs and risk of myocardial infarction: a case-control study in Finnish farmers. *International Journal of Epidemiology, 25*, 760-762.

M Personne, G Sjoberg, H Persson. Citalopram overdose-review of cases treated in Swedish hospitals. Clin Tox, 1997; 35(3), 237-240.

M Personne, G Sjoberg, H Persson. Citalopram toxicity. Lancet 1997; 350: 518-519.

Peselow, E. D., Filippi, A. M., Goodnick, P., Barouche, F., & Fieve, R. R. (1989). The short- and long-term efficacy of paroxetine HCl: A. Data from a 6-week double-blind parallel design trial vs. imipramine and placebo. *Psychopharmacology Bulletin*,25, 267-271.

Peterson-Homer, L.(Ed) (1998) Special section: Empirically Supported Psychological Therapies. *Journal of Consulting and Clinical Psychology* 66 (1) 3-125

Pignone, M. P., Gaynes, B. N., Rushton, J. L., Burchell, C. M., Orleans, C. T., Murlow, C. D.,& Lohr, K. N. (2002). Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med, 136*, 765-76.

Plummer, S., Ritter, S.A.H., Leach, R.E., Mann, A.H. & Gournay, K.J. (1997) A controlled comparison of the ability of practice nurses to detect psychological distress in patients who attend their clinics. *Journal of Psychiatric and Mental Health;Nursing,* 4: 221-223.

Pollock, B. G., Laghrissi-Thode, F., Wagner, W. R. (2000). Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. *Journal of Clinical Psychopharmacology, 20*, 137-140.

Posternak, MA, Miller I. (2001). Untreated short-term course of major depression: a meta-analysis of outcomes from studies using wait-list control groups. *Journal of Affective Disorders* 66: 139-146.

Pratt, L. A., Ford, D. F., Crum, R. M. et al. (1996). Depression, psychotropic medication and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. *Circulation, 94*, 3123-3129.

Price, L. H., Carpenter, L. L., Rasmussen, S. A. (2001). Drug combination strategies. In Amsterdam,J.D., Hornig,M. & Nierenberg,A.A. (Eds.) (2001) *Treatment Resistant Mood Disorders* (pp194-222). Cambridge: Cambridge University Press.

Priest RG, Vize C, Roberts A, Roberts M & Tylee A (1996). Lay people's attitudes to treatment of depression: results of opinion poll for Defeat Depression Campaign just before its launch. *BMJ* 1996; 313: 858-859.

Proudfoot, J., Goldberg, D. P., Mann, A., Everitt, B., Marks, I. M. & Gray, J. A. (2003). Computerised, interactive, multimedia cognitive behavioural therapy for anxiety and depression in general practice. *Psychological Medicine, 33*, 217-227.

Proudfoot, J., Guest, D., Carson, J., Gray, J. A. (1997) Effect of cognitive-behavioural training on job-finding among long-term unemployed people. *The Lancet* 350(9071):96-100.

Pyne JM, Bullock D, Kaplan RM, et al. (2001) Health-related quality-of-life measure enhances acute treatment response prediction in depressed inpatients. *J Clin Psychiatry*; 62: 261-268

Pyne JM, Patterson TL, Kaplan RM, et al. (1997) Preliminary longitudinal assessment of quality of life in patients with major depression. *Psychopharmacology Bulletin*; 33(1): 23-29

Quitkin FM. Harrison W. Stewart JW. McGrath PJ. Tricamo E. Ocepek-Welikson K. Rabkin JG. Wager SG. Nunes E. Klein DF. (1991) Response to phenelzine and imipramine in placebo nonresponders with atypical depression. A new application of the crossover design. *Archives of General Psychiatry. 48(4):319-23*

Quitkin, F. M., Rabkin, J. G., Gerals, J., Davis, J. M., Klein, D. F. (2000). Validity of Clinical Trials of Antidepressants. *American Journal of Psychiatry, 157(3),* 327-337.

Rabkin, J. G., Markowitz, J. S., Stewart, J. W., McGrath, P. J., Harrison, W., Quitkin, F. M., & Klein, D. F. (1986). How blind is blind? Assessment of patient and doctor medication guesses in a placebo-controlled trial of imipramine and phenelzine. *Psychiatry Research, 19, 75-86*
cited by Kirsch,I., Moore,T.J., Scoboria,A. & Nicholls,S.S. (2002) The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment 5.*

Ramachandani P & Stein A (2003) The impact of parental psychiatric disorder on children. *BMJ*; 327: 242-243.

Rasmussen, S. L., Overo, K. F., Tanghoi, P. (1999). Cardiac safety of citalopram: prospective trials and retrospective analyses. *Journal of Clinical Psychopharmacology, 19(5)*, 407-415.

Rector, N. A., Bagby, R. M., Segal, Z. V., Joffe, R. T., & Levitt, A. (2000). Self-criticism and dependency in depressed patients treated with cognitive therapy or pharmacotherapy. *Cognitive Therapy & Research*, 24, 571-584.

Reilly, J. G., Ayis, S. A., Ferrier, I. N., Jones, S. J., & Thomas, S. H. (2000). QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet, 25, 355(9209*), 1048-1052.

Revicki, D.A., Wood, M. (1998) Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications. *Journal of Affective Disorders, 48*:25-36

Rogers, C. R. (1957). The necessary and sufficient conditions of therapeutic personality change. *Journal of Consulting Psychology*, 21, 95-103.

Rogers, C. R. (1986). Rogers, Kohut and Erikson. *Person-Centred Review*, 2, 375-377.

Roose, S. P. (2001). Depression, anxiety, and the cardiovascular system: the psychiatrist's perspective. *Journal of Clinical Psychiatry, 62(Suppl.8)*, 19-22.

Roose, S. P. (2003). Treatment of depression in patients with heart disease. *Biological Psychiatry, 54,* 262-268.

Roose, S. P., Glassman, A. H. (1989). Cardiovascular effects of TCAs in depressed patients with and without heart disease. *Journal of Clinical Psychiatry Monograph, 7(2*), 1-19.

Roose, S. P., Laghrissi-Thode, F., Kennedy, J. S., Nelson J. C., Bigger, J. T. Jr., Pollock, B. G., et al. (1997). A comparioson of paroxetine to nortriptyline in depressed patients with IHD. *Journal of the American Medical Association, 279*, 287-291.

Roose, S.P., Glassman, A. H., Giardina, E. G. V. et al. (1987). Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Archives of General Psychiatry, 44*, 273-275.

Roose SP, Glassman AH, Attia E, Woodring S, Giardina E-GV, Bigger JT Jr (1998) Cardiovascular effects of fluoxetine in depressed patients with heart disease. *American Journal of Psychiatry.* 155(5):660-665

Rose, D., Fleischmann, P., Wykes, T., Leese, M., and Bindman, J. (2003) Patients' perspectives on electroconvulsive therapy: systematic review *BMJ*; 326 (7403): 1363.

Rosenbaum, J. F., Fava, M., Hoog, S. L. et al. (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: a randomised controlled trial. *Biological Psychiatry, 44*, 77-88.

Ross, D. C., Quitkin, F. M. & Klein, D. F. (2002). A typological model for estimation of drug and placebo effects in depression. *Journal of Clinical Psychopharmacology, 22(4*), 414-8.

Rost K. Williams C. Wherry J. Smith GR Jr. (1995) The process and outcomes of care for major depression in rural family practice settings. *Journal of Rural Health*. 11(2):114-21

Roter DL, Hall JA, Kern DE, Barker R, Cole KA, Roca RP.(1995) Improving physicians interviewing skills and reducing patients' emotional distress. *Arch Intern Med 155*:1877-84

Roth, A. & Fonagay, P. (1996). *What Works for Whom: A Critical Review of Psychotherapy Research*. New York: Guilford.

Rothschild, A. J. (2003). Challenges in the treatment of depression with psychotic features. *Biol Psychiatry, 53*, 680-690.

Royal College of Psychiatrists. (1997). Benzodiazepines: risks, benefits or dependence: a re-evaluation. *Council Report CR57*. Royal College of Psychiatrists: London.

Ryle, A. (1989) *Cognitive Analytic Therapy: Active Participation in Change. A New Integration in Brief Psychotherapy (Wiley Series on Psychotherapy and Counselling).* Chichester. John Wiley & Sons

Safran, J. D & Muran, J. C. (2000). *Negotiating the Therapeutic Alliance: A Relational Treatment Guild*. New York: Guilford.

Salamone, J. D. (2000). A critique of recent studies on placebo effects of antidepressants: importance of research on active placebos. *Psychopharmacology, 152*, 1-6.

Salkovskis, P. (2002). Empirically grounded clinical interventions. *Behavioural and Cognitive Psychotherapy,* 30, 1-2.

Sartorius, N. (2001) The economic and social burden of depression. *J Clin Psychiatry*, 62, (suppl 15): 8-11

Sartorius N. (2002) One of the last obstacles to better mental health care: The stigma of mental illness. Neuropsychiatrie 16(1-2) (5-10),

Sashidharan S, Surtees P, Kreitman N, Ingham J, Miller P (1988) Hospital and general population morbidity from affective disorders: a comparison of prevalence and inception rates. *British Journal of Psychiatry 152*, 499 - 505

Sauer, W. H., Berlin, J. A., Kimmel, S. E. (2001). Selective serotonin reuptake inhibitors and myocardial infarction. *Circulation, 104*, 1894-1898.

Schneider, L. S. Small, G. W. (2002). The increasing power of placebos in trials of antidepressants. *Journal of Psychopharmacology, 11 (suppl.4),* 33-37.

Schulberg, H. C., Block, M. R., Madonia, M. J., Scott, C. P., Rodriguez , E., Imber, S. D., Perel, J., Lave, J., Houck, P. R., Coulehan, J. L. (1996). Treating major depression in primary care practice. Eight-month clinical outcomes. *Archives of General Psychiatry, 53,* 913-919.

Schulberg, H. C., Katon, W.J., Simon, G. E., Rush, A. J. (1999). Best clinical practice: guidelines for managing major depression in primary medical care. *Journal of Clinical Psychiatry, 60(Suppl 7),* 19-26.

Scott, A.I.F., Freeman, C.P.L. (1992) Edinburgh primary care depression study: treatment outcome, patient satisfaction, and cost after 16 weeks. *BMJ, 304*:883-887

Scott, J., Moon, C.A.L., Blacker, C.V.R., et al. (1994) A.I.F. Scott & C.P.L. Freeman's "Edinburgh Primary Care Depression Study". *British Journal of Psychiatry, 164*:410-415

Scott, J., Palmer, S., Paykel, E. et al. (2003) Use of cognitive therapy for relapse prevention in chronic depression. *British Journal of Psychiatry, 182*: 221-227

Scottish Intercollegiate Guidelines Network (2001). *SIGN 50: A guideline developer's handbook*. Edinburgh: Scottish Intercollegiate Guidelines Network.

Segal, Z. V., Whitney, D. K., Lam, R. W. & the CANMAT Depression Work Group. (2001a). Clinical Guidelines for the Treatment of Depression Disorders. III. Psychotherapy. *The Canadian Journal of Psychiatry*, 29S-37S.

Segal, Z., Kennedy, S. H., Cohen, N. L. and the CANMAT Depression Work Group. (2001b). Clinical Guidelines for the Treatment of Depressive Disorders. V. Combining psychotherapy and pharmacotherapy. *The Canadian Journal of Psychiatry*, 59S – 62S.

Selmi PM, Klein MH, Greist JH, Sorrell SP, Erdman HP. (1990) Computer-administered cognitive-behavioural therapy for depression. *Am J Psychiatry* 147:51-56.

Senra, C. (1995) Measures of treatment outcome of depression: an effect-size comparison. *Psychological Reports, 76*, 187-192.

Serby M & Yu M (2003). Overview: Depression in the Elderly. *Mount Sinai Journal of Medicine*, 70: 38-44

Shaap, C., Bennun, I., Schindler, L. & Hoogduin, K. (1993). *The Therapeutic Relationship in Behavioural Therapy.* Chichester: Wiley.

Shah, R., Uren, Z., Baker, A., & Majeed, A. (2001). Trends in deaths from drug overdose and poisoning in England and Wales 1993-1998. *Journal of Public Health Medicine, 23*, 242-246.

Shapiro DA, Barkham M, Rees A, Hardy GE, Reynolds S, Startup M, (1994) 'Effects of treatment duration and severity of depression in the maintenance of gains following cognitive/behavioural and psychodynamic/interpersonal psychotherapy', *J Consult Clin Psychology*, 62 (3), 522-534 [version I – cut-offs from unpublished manuscript by Beck (1978, Beck Depression Inventory, Unpublished Manuscript, University of Pennsylvania)

Sheikh, A.A. & Sheikh, K.S. (Eds.) (1989). *Healing East and West: Ancient Wisdom and Modern Psychology*. New York: Chichester.

Shelton & Tollefson.(1999). *12th Annual Meeting of European college of neuropsychopharmacology, London, Sept, 19, 1999.*

Simon GE, Goldberg DP, Von Korf M & Ustun TB (2002) Understanding cross national differences in depression prevalence. *Psychological Medicine 32,* 585-594

Simon, G.E., VonKorff, M., Heiligenstein, J.H. et al. (1996). Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. *Journal of the American Medical Association, 275*, 1897-1902.

Simpson, S., Corney, R, Fitzgerald, P., Beecham, J. (2000) A randomized controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression. *Health Technology Assessment (Winchester, England). 4(36):1-83*

Smith, D., Dempster, C., Glanville, J., Freemantle, N. & Anderson, I. (2002). Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: A meta-analysis. *British Journal of Psychiatry 180*, 396-404.

Sotsky, S. M., Glass, D. R., Shea, M. T., Pilkonis, P. A., Collins, J. F., Elkin, I., Watkins, J. T., Imber, S. D., Leber, W. R., Moyer, J. & Oliveri, M. E. (1991). Patient predictors of response to psychotherapy and pharmacotherapy: Findings in the NIMH Treatment of Depression Collaborative Research Program. *American Journal of Psychiatry, 148*, 997-1008.

Stassen H. H., Angst J., Delini-Scula, A. (1994). Severity at baseline and onset of improvement in depression: meta-analysis of imipramine and moclobemide versus placebo. *European Psychiatry, 9*,129-136.

Stein LI. Test MA. (1980) Alternative to mental hospital treatment. I. Conceptual model, treatment *Archives of General Psychiatry*. 37(4):392-7

Steiner,M. (1978) Failure of L-triiodothyronine (T3) to potentiate tricyclic antidepressant response. *Current Therapeutic Research, Clinical & Experime*ntal.23(5II):655-659,

Stewart, A. (1994) Antidepressant pharmacotherapy: cost comparison of SSRIs and TCAs. *British Journal of Medical Economics 7*:67-79

Stewart, A. (1996) Revisiting the relative cost-effectiveness of selective serotonin re-uptake inhibitors and tricyclic antidepressants: what price inflation and subtherapeutic dosages? *British Journal of Medical Economics, 10*:203-216

Stiles, W.B., Leach, C., Barkhan, M., Lucock, M., Iveson, S., Shapiro, D.A., Iveson, M., & Hardy, G.E., (2003) Early sudden gains in psychotherapy under routine clinical conditions: practiced based evidence. *Journal of Consulting and Clinical Psychology*, 71, 14-21

Strik JJ. Honig A. Lousberg R. Lousberg AH. Cheriex EC. Tuynman-Qua HG. Kuijpers PM. Wellens HJ. Van Praag HM.(2000) Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. *Psychosomatic Medicine.* 62(6):783-9

Sullivan, H.S. 1953. *The interpersonal theory of psychiatry.* New York: W. Norton

Tamminga, C. A., Nemeroff, C. B., Blakely, R. D., Brady, L., Carter, C. S., Davis, K. L. et al. (2002). Developing novel treatments for mood disorders: Accelerating discovery. *Biol Psychiatry, 52*, 589-609.

Taylor, D. (1995). Selective Serotonin Reuptake Inhibitors and tricyclic antidepressants in combination: interactions and therapeutic uses. *British Journal of Psychiatry, 167*, 575-580.

Taylor, D., Paton, C., & Kerwin, R. (2003). *The Bethlem & Maudsley NHS Trust*: *Maudsley Prescribing Guidelines* (7th ed) London: Martin Dunitz Publishers

Teasdale, J. D., Moore, R. G., Hayhurst, H., Pope, M., Williams, S., & Segal, Z. V (2002). Metacognitive awareness and prevention of relapse in depression: Empirical evidence. *Journal of Consulting & Clinical Psychology*, 70, 275-287.

Thase,M.E.; Kupfer,D.J.; Jarrett,D.B. (1989) Treatment of imipramine-resistant recurrent depression: I. An open clinical trial of adjunctive L-triiodothyronine. *Journal of Clinical Psychiatry* 50(10):385-8

Thase, M. (2002). Studying New Antidepressants: If there was light at the end of the tunnel, could we see it? *Journal of Clinical Psychiatry, 63*, 24–27.

Thase, M. E., Frank, E., Kornstein, S. G., & Yonkers, K. A. (2000). Gender differences in response to treatments of depression, in gender and its effect on psychopharmacology. In Frank, E. (Ed). (2000). *Gender and its effects on psychopathology*. *American Psychopathological Association series.* pp103-129. Washington, DC: American Psychiatric Publishing, Inc

Thase, M. E., Mallinger, A. G., McKnight, D. et al. (1992). Treatment if imipramine-resistant recurrent depression. IV: a double-blind cross over study of tranylcypromine for anergic bipolar depression. *American Journal of Psychiatry, 149*, 195-198.

Thase, M. E., Rush, A.J. (1997). When at first you don't succeed: sequential strategies for antidepressant non-responders. *Journal of Clinical Psychiatry, 58 (suppl.13)*, 23-29.

Thompson C, Thompson CM. (1989) The prescribing of antidepressants in general practice: II. A placebo-controlled trial of low-dose dothiepin. *Human Psychopharmacology* 4(3):191-204.

Thompson C, Kinmonth A-M, Stevens L, Peveler RC, Stevens A, Ostler KJ, Pickering RM, Baker NG, Henson A, Priece J, Cooper D, Campbell MJ. (2000). Effects of good practice guidelines and practice based education on the detection and treatment of depression in primary care. *Lancet;* 355: 185

Thompson C, Ostler K, Peveler RC, Baker N, Kinmonth AL. (2001) Dimensional perspective on the recognition of depressive symptoms in primary care: The Hampshire Depression Project 3. *Br J Psychiatry*.179:317-23.

Thorogood, M., Cowen, P., Mann, J., Murphy, M., & Vessey, M. (1992). Fatal myocardial infarction and use of psychotropic drugs in young women. *Lancet, 340*, 1067-1068.

Thornen, P., Floras, J. S., Hoffman, P., Seals, D. R. (1990). Endorphins and exercise: physiological mechanisms and clinical implications. *Medical Science, Sports and Exercise,* 22, 417-428.

Tiemens B, Ormel J, Jenner JA, Meer K, van Os TW, van den Brink, R.H.S. Smit, J., (1999). Training primary-care physicians to recognize, diagnose and manage depression: does it improve patient outcomes? *Psychological Medicine,* 29, 833-845.

Tolliver, L.M., 1993. Social and mental health needs of the aged. *American Psychologist*. 38, 316-318.

Tome MB, Isaac MT. (1998) Cost effectiveness study of a year follow-up of selective serotonin reuptake inhibitor (SSRI) and augmentor combination compared with SSRI and placebo. *Int Clin Psychopharmacology*; 13:175-182

Truax, C. B., & Carkhuff, R. (1967). *Toward Effective Counselling in Psychotherapy*. Chicago: Aldine.

Tylee, A. (2001) Major depressive disorder (MDD) from the patient's perspective: overcoming barriers to appropriate care. *International Journal of Psychiatry in Clinical Practice* 5 (supplement), s37-s42

U. S. Preventive Services Task Force, 1996

Ustun,T.B. & Sartorius,N. (Eds).(1995) *Mental illness in General Health Care: An international study.* Chichester: Wiley.

van Os TW van den Brink RH, Tiemens BG, Jenner JA, van der Meer K, Ormel J (2002) Are Effects Of Depression Management Training For General Practitioners On Patient Outcomes Mediated By Improvements In The Process Of Care? *** (in press)

Velazquez, C., Carlson, A., Stokes, K. A., & Leikin, J. B. (2001). Relative safety of mirtazapine overdose. *Vet Hum Toxicol, 43(6),* 342-344.

Vize, C.M., & Priest, R.G. (1993). Defeat Depression Campaign: attitudes to depression. *Psychiatric Bulletin, 17*, 573-574.

Von Korff M. Goldberg D. (2001) Improving outcomes in depression: the whole process of care needs to be enhanced. *British Medical Journal*. 323(7319):948-9

Wagner, H., Bladt , S. (1994). Pharmaceutical quality of Hypericum extracts. *J Geriatr Psychiatry Neurol, 7(suppl 1),* S65-68.

Walraven, C., Mandani, M. M., Wells, P.S. (2001). Inhibition of serotonin reuptake by antidepressants and upper gastro-intestinal bleeding in elderly patients: retrospective cohort study. *British Medical Journal*, 323, 655-660.

Walsh, B. T., Seidman, S. N., Sysko, R., & Gould, M. (2002). Placebo response in studies of major depression: variable, substantial, and growing. *The Journal of the American Medical Association, 287(14)*, 1840-1847.

Wampold, B. E., Minami, T., Baskin, T. W., & Tierney, S. C. (2002). A meta-(re)analysis of the effects of cognitive therapy versus 'other therapies' for depression. *Journal of Affective Disorders*, 68, 159-165.

Weissman MM. Bland R. Joyce PR. Newman S. Wells JE. Wittchen HU. (1993) Sex differences in rates of depression: cross-national perspectives. *Journal of Affective Disorders*. 29(2-3):77-84

Weissman, M. M., Markowitz, J. C., & Klerman, G. L. (2000). *Comprehensive Guide to Interpersonal Psychotherapy*. New York: Basic Books.

Wells KB, Sherbourne C, Schoenbaum M, Duan N, Meredith L, Unutzer J, Miranda J, Carney MF, Rubenstein LV. (2000) Impact of disseminating quality improvement programs for depression in managed primary care: a randomized controlled trial. *JAMA*;283(2):212-220.

West,R. (1992) *Depression*. London: Office of Health Economics. pp 1 - 40

Whalley, D., McKenna, S.P. (1995) Measuring quality of life in patients with depression or anxiety. *Pharmacoeconomics, 8(4)*: 305-315

Wheeler, J. G., Christensen, A., & Jacobson, N. S. (2001). Couples distress. In D. H. Barlow (Ed.), *Clinical Handbook of Psychological Disorders* (p. 609-630). New York: Guilford.

Whooley, M. A., Avins, A. L., Miranda, J., Browner, W. S. (1997). Case-finding instruments for depression: two questions as good as many. *J Gen Intern Med, 12*, 439-445.

Whyte, I. M., Dawson, A. H., & Buckley, N. A. (2003). Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants.*QJM*, 96(5), 369-374.

Wiersma D, Kluiter H, Nienhuis F, Ruphan M, Giel R. (1989) *Day-treatment with community care as an alternative to standard hospitalization: an experiment in the Netherlands. A preliminary communication*; Department of Social Psychiatry, University of Groningen

Wilfley, D.E, MacKenzie, K.R., Welch, R.R., Ayres, V.E. and Weissman, M.M. 2000. *Interpersonal psychotherapy for groups.* New York: Basic Books

Williams JW Jr, Kerber CA, Mulrow CD, Medina A, Aguilar C. Depressive disorders in primary care: prevalence, functional disability, and identification. *J Gen Intern Med.* 1995;10:7-12)

Wilmink F (1989) *Patient, physician, psychiatrist. An assessment of mental health problems in primary care.* Glimmen, The Netherlands, Phais

Wilson, K., Mottram, P. Sivanranthan, A., & Nightingale, A. (2001). Antidepressant versus placebo for depressed elderly (Cochrane Review). In: *The Cochrane Library, Issue 2,* Oxford: Update software.

Winokur, G., Corell, W., & Keller, M. (1993). A prospective study of patients with bipolar and unipolar affective disorder. *Arch Gen Psychiatry, 52*, 367-373.

Wolpe, J. (1971). Neurotic depression: Experimental analogue, clinical syndromes and treatment. *American Journal of Psychotherapy*, 25, 362-368.

Wolpe, J. (1979). The experimental model and treatment of neurotic depression. *Behaviour Research and Therapy*, 17, 555-56.

Woods SW, Rizzo JA. (1997) Cost-effectiveness of antidepressant treatment reassessed. *British Journal of Psychiatry*; 170:257-263

World Bank (1993) *World Development Report: Investing in Health Research Development.* Geneva: World Bank

World Health Organisation. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines*. Switzerland: WHO

World Health Organisation. (2001) *World Health Report 2001: Mental Health: New Understanding, New Hope*. Geneva, Switzerland: WHO

Young, J. E., Weinberger, A. D., & Beck, A. T (2001). Cognitive therapy for depression. In, D. H Barlow (Ed.), *Clinical Handbook of Psychological Disorders* (p. 264-308). New York. Guilford.

Zajecka, J., Fawcett, J., Amsterdam, J. et al. (1998). Safety of abrupt discontinuation of fluoxetine: a randomised placebo-controlled study. *Journal of Clinical Psychopharmacology, 18*, 193-197.

Zung, W. W. K. (1965). A self rating depression rating scale. *Arch Gen Psychiatry, 12*, 63-70.