

Effective

HEALTH CARE

The Treatment of Depression in Primary Care

Which treatments are
effective in the management
of depression in primary
care?

▶ Depression affects a majority of people at some time in their lives and is strongly associated with social and economic circumstances.

▶ The classification of *major depressive episode* is important in treatment. Half the cases of *major depression* are unrecognised in primary care, especially where the patient presents with physical symptoms.

▶ Suicide rates are higher in people with depression, but it is not possible to predict which primary care attenders with depression are likely to commit suicide. Educational programmes for general practitioners may improve the detection and management of depression and help reduce suicide rates.

▶ Antidepressants are generally effective in the treatment of *major depression* but a significant number of patients drop out of treatment and many patients will relapse.

▶ The selective serotonin reuptake inhibitors (SSRIs) are of similar efficacy and have similar drop-out rates to other cheaper antidepressants, and their widespread use as the routine first-line treatment in *major depression* could result in an increase in the NHS drug budget for antidepressants in England of over £100m a year.

▶ A range of non-drug therapies such as cognitive therapy, psychotherapy, social work support and counselling is used for the treatment of major depression. Cognitive therapy has been shown to be as effective as usual treatment in primary care. Counselling is increasingly available in primary care, but requires evaluation as an intervention for depression.

▶ Further research is required to provide evidence on the effectiveness of a variety of management strategies for depression.

A. DEPRESSION IN PRIMARY CARE

Depression affects a majority of people at some time in their lives and is strongly associated with social and economic circumstances. The classification of *major depressive episode* is important in treatment. Half the cases of *major depression* are unrecognised in primary care, especially where the patient presents with physical symptoms.

A.1 Around 60–70% of adults will at some time experience depression or worry of sufficient severity to influence their daily activities.¹ For the majority of people episodes of depression are short-lived, but a minority experience a range of severe psychological and physical symptoms which may persist.

A.2 Depression is one of the most common single reasons for attending a general practitioner (GP), and the majority of depressed people who receive treatment do so in the primary care setting.² Depression results in a major burden of suffering among patients and their families. The cost of depression to the NHS and to society is considerable.^{3–5}

Major depression

A.3 *Major depressive episode* Clinicians have found it useful to identify a subgroup of people who are categorised as having a *major depressive episode*^{6–8} using criteria like those summarised in Table A.1.

The *Effective Health Care* bulletins are based on a systematic review and synthesis of literature on the clinical effectiveness, cost-effectiveness and acceptability of health service interventions. Relevant and timely topics for review are selected by a Steering Group comprising managers, directors of public health and academics. Selection of topics takes into account the following criteria: resource implications, uncertainty about effectiveness, and the potential impact on health. The review and synthesis of the literature is carried out by a research team using established methodological checklists, with advice from expert consultants for each topic. The bulletins represent the views of the *Effective Health Care* research team.

A.4 The diagnosis of *major depressive episode* is commonly used in research and clinical practice as a criteria for treatment.^{6–8} The DSMIII-R category of *major depression* (see Appendix I) is summarised in Table A.1.

Table A.1 Summary of DSMIII-R criteria for major depression (for more detailed criteria see Appendix I).

At least five of the following symptoms present during the same two-week period. This must include at least one of the symptoms *depressed mood* or *diminished interest or pleasure*.

1. Depressed mood
2. Markedly diminished interest or pleasure in normal activities
3. Significant weight loss or gain
4. Insomnia or hypersomnia
5. Agitated or retarded
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death or suicidal thoughts/actions

A.5 Episodes of *major depression* are around twice as common among women as men,¹ peak in middle age, and are strongly associated with adverse social and economic circumstances such as unemployment, divorce or separation, inadequate housing and lower social class.²

A.6 Up to 50% of general practice attenders may have some depressive symptoms,⁹ of whom around 5% will have *major depression*.^{10–15}

A.7 Around half of patients with *major depression* are routinely recognised by GPs,¹⁶ although much higher rates of detection have been reported,¹⁷ indicating the potential for case finding in general practice. Training¹⁸ and the use of routine screening instruments^{19,20} can improve the ability of GPs to detect *major depression* amongst practice attenders, and there is evidence that early detection and treatment may reduce the likelihood that the condition will persist.²¹

A.8 The importance of improving identification, diagnosis and appropriate treatment of people with depression has long been recognised and is the subject of the *Defeat Depression* campaign involving the Royal Colleges of General Practitioners and Psychiatrists, which aims to improve interventions for people with depression.²²

A.9 Patients with *major depression* often present with predominantly physical (somatic) symptoms²³ (eg Table A.1, items 3–6). In addition, many patients with *major depression* also have a physical illness.²⁴ Depression in the presence of physical symptoms is more likely to remain unidentified by GPs.¹⁶

A.10 Depression and anxiety often present together, but anxiety will often resolve when a patient is treated appropriately for depression.²⁵

B. SUICIDE

Suicide rates are higher in people with depression, but it is not possible to predict which primary care attenders with depression are likely to commit suicide. Educational programmes for GPs may improve the detection and management of depression and help reduce suicide rates.

B.1 Suicide rates are higher in people with depression, but it is not possible to predict with any accuracy which primary care attenders will commit suicide.²⁶⁻³¹

B.2 A recent quasi-experimental study on the island of Gotland (Sweden) reported that the rate of suicide was reduced after the introduction of training programmes for GPs.^{32,33} The reduction in suicide rate was accompanied by an improvement in other indicators of quality of care and a saving in drug and hospital care which outstripped the cost of the programme more than thirty-fold.

B.3 The Gotland study did not, however, have a matched control group and it is unclear to what extent the improved outcomes can be attributed to the educational campaign. In addition, as the suicide rate in Sweden at the time of the study was more than double that in England and Wales³⁴ the potential impact of introducing such a programme in Britain may be less. More generally, it is hard to assess the degree to which the results of the programme can be generalised to the British primary care setting.

B.4 Because it has been estimated that 40–50% of all suicides are committed by patients with undiagnosed or inadequately treated depressive disorders,^{35,36} research is urgently required to examine the effectiveness of GP educational strategies in Britain which can conclusively demonstrate whether the changes seen in Gotland can be attributed to such programmes.

C. EVALUATING THE EFFECTIVENESS OF TREATMENTS

Well-designed randomized controlled trials provide the most reliable evidence for the effectiveness of interventions, but there are a number of difficulties with the design of available trials.

C.1 Well-designed randomised controlled trials (RCTs) provide the most reliable evidence for the efficacy of therapeutic interventions.³⁷ However, trials often include a heterogeneous group of patients, with different durations of illness, past histories and past treatments. Avoiding bias by keeping the subjects and assessors unaware of treatment received (blinding) is also problematic. There are difficulties in defining the

content of non-drug interventions and in identifying suitable controls.

C.2 *Outcome measures* Several instruments are used in the measurement of severity and outcome.³⁸⁻⁴² These provide information about different aspects of depression. Most trials use several instruments, and the Hamilton Depression Rating Scale (HAMD) is used most consistently. The HAMD is reliable but is weighted towards change in somatic symptoms rather than psychological and cognitive factors.⁴³ Studies should more consistently use the wider range of patient-centred outcome measures which are available when evaluating and monitoring treatment.

C.3 *Improvement among people receiving no formal treatment* Patients receiving general support but no formal treatment from their GPs showed a mean improvement in HAMD at 4 weeks of 40–45% and 60% at 6 weeks.⁴⁴⁻⁴⁶

C.4 *Analysis of results* Most trials have significant drop-out rates but intention-to-treat analysis (ie by initial randomisation to treatment) is rarely undertaken. Analysis of the results of treatment completers only will give biased estimates of efficacy as drop-out is non-random.⁴⁷

C.5 *General application* Results obtained under the strict conditions of a clinical trial may not be generally applicable to usual clinical settings.⁴⁸ Patients with *major depression* treated by GPs may differ in severity and symptom pattern to those with the same diagnosis treated in psychiatric outpatients.^{49,50} Prescribing behaviour may also differ between settings.^{51,52}

C.6 There are twelve RCTs in a British general practice setting which compare either drug treatment with no active treatment or drug treatment with non-drug treatment^{45-46,53-62} (See Appendix II). A primary care trial from Australia⁴⁴ is also informative because of the similarities between general practice in Australia and the UK.

D. DRUG TREATMENTS

Antidepressants are generally effective in the treatment of *major depression* but a significant number of patients drop out of treatment and many patients will relapse. The SSRIs are of similar efficacy and have similar drop-out rates to other available antidepressants. Their widespread use as the routine first-line treatment in *major depression* could result in an increase in the NHS drug budget for antidepressants in England of over £100m per year.

D.1 Tricyclic and related antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs) are the two main groups of antidepressant drugs in common

Table D.1 Cost of drug treatment

	Defined Daily Dosage (mg) ¹⁶²	28-day Cost (£)*	Side-effects and Cautions†	Risk in Overdose‡
<i>Older Tricyclics</i>				
Amitriptyline	75	1.31	AM, G, I, Sed, W	High
Amoxapine	150	14.76	AM, G, I, L-Sed, W	High
Clomipramine	100	7.71	AM, G, I, L-Sed, W	Moderate
Desipramine	100	3.99	AM, G, I, L-Sed, W	High
Dothiepin	75	3.91	AM, G, I, Sed, W	High
Doxepin	100	3.18	G, I, L-AM, Sed, W	High
Imipramine	100	1.74	AM, G, I, L-Sed, W	High
Nortriptyline	75	5.99	AM, G, I, L-Sed, W	High
Protriptyline	30	3.08	AM, G, I, Stim, W	Moderate
Trimipramine	150	14.08	AM, G, I, Sed, W	High
<i>Newer Tricyclics and Related</i>				
Lofepramine	105	7.48	G, I, L-AM, L-Sed, W	Low
Matprotiline	100	6.06	G, I, L-AM, Sed, W	High
Mianserin	60	10.96	BC, G, I, L-AM, Sed, W	Low
Trazodone	300	30.33	G, I, L-AM, Sed, W	Moderate
Viloxazine	200	7.11	G, I, L-AM, L-Sed, W	Low
<i>Selective Serotonin Reuptake inhibitors</i>				
Fluoxetine	20	29.91	I, J, L-Sed	Low
Fluvoxamine	150	35.00	I, J, L-Sed	Low
Paroxetine	20	31.64	I, J, L-Sed	Low
Sertraline	75	38.13	I, J, L-Sed	Low

Notes

- AM antimuscarinic
 - BC Blood count monitoring required, risk of haematological and hepatic reactions
 - G general: dry mouth, blurred vision, constipation, nausea, urinary retention, sweating, cardiovascular disturbance, hypomania, weight gain, interference with sexual function, occasional heart block and arrhythmias
 - I may impair performance at skilled tasks
 - J diarrhoea, nausea, vomiting, dry mouth, insomnia, sexual dysfunction, tremor, sweating but few antimuscarinic effects
 - L- less, eg L-Sed: less sedating
 - Sed sedative
 - Stim stimulant action
 - W withdrawal: reduction in dosage recommended over a period of four weeks
- * Estimated weighted average across all prescriptions
 † Source: *British National Formulary, September 1992*
 ‡ Primary source: Prescription Pricing Authority Data, 1990

use in general practice (see Table D.1). Tricyclic antidepressants were first introduced in 1959 and are the most commonly used; newer tricyclic and related drugs have subsequently been developed which are generally less toxic and have modified side-effects profiles.⁶⁴ The SSRIs are a recent development and their rapidly increasing use is controversial⁶³ (see Figure 1) and has major cost implications (see Figure 2).

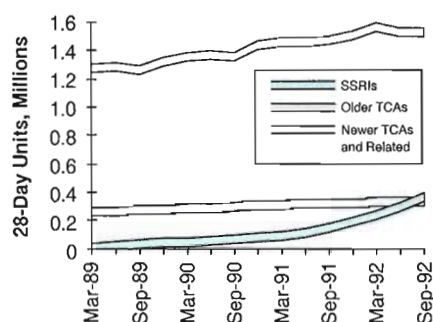
Tricyclic and related antidepressants

D.2 The trials conducted in primary care show that a

range of tricyclic antidepressants are effective in the treatment of *major depression* when used in recognised therapeutic doses. Amitriptyline has been most extensively evaluated and produces a 50-100% improvement compared with placebo in HAMD at 4-6 weeks.^{44,45,53} Low dose regimens are much less effective and may not be superior to placebo.^{44-46,53,55,62}

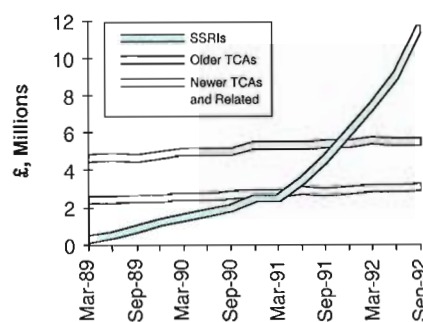
D.3 Patients with the mildest depression do not respond well to tricyclic medication.^{53,65} Severity of depressive episode is the most powerful predictor of benefit from treatment among outpatients.^{65,66} In the majority of cases *major depression* resolves with treat-

Figure 1: Quarterly Volume of Use of NHS Prescribed Antidepressants, in England



Sources: Prescription Pricing Authority data, 1989-92. World Health Organisation, 1992.¹⁶²

Figure 2: Quarterly Total NHS Antidepressant Prescribing Costs, in England



Source: Prescription Pricing Authority data, 1989-92.

ment, but around 12–15% of patients with the condition will have symptoms for a period of two years or more.^{67,68}

D.4 Relapse Relapse is a serious problem and around half of patients whose symptoms have resolved relapse within a year of the cessation of treatment.^{69,70} Evidence from RCTs examining the outpatient treatment of patients with *major depression* indicates that continued treatment with antidepressants for several months after the episode has resolved reduces relapse.⁶⁹⁻⁷² Further research is required to examine the effectiveness of continuation treatment in primary care.

D.5 Response to tricyclic antidepressants has been shown not to depend upon demographic variables (age, sex, social class), previous history of depression, apparent cause (endogenous/reactive),⁷³ or the presence or absence of social stress.⁴⁴ Treatment with tricyclic and related antidepressants produces a parallel reduction in anxiety and improves sleep.^{44,46,53,55,62}

Selective serotonin reuptake inhibitors

D.6 The SSRIs have a different side-effects profile to tricyclic and related antidepressants. They are less toxic than the older tricyclics, relatively expensive (see Table D.1), and are currently being heavily promoted as the first-line treatment in major depression.⁷⁴⁻⁷⁷

D.7 Efficacy and comparison with other drugs Sixty-four RCTs were identified which compare SSRIs with tricyclic or related antidepressants.⁷⁸⁻¹⁴¹ These trials were in the outpatient, inpatient and primary care setting. Analysis of the 20 studies which report sufficient detail for pooling (meta-analysis) shows that SSRIs have a similar efficacy to the tricyclic antidepressants.¹⁴² However, many of the trials comparing SSRIs and tricyclic and related drugs have small numbers and do not fully report the results and follow-up is only for a few weeks. There is no good evidence identifying subgroups of patients with *major depression* for whom SSRIs may be more effective than other, cheaper treatments.

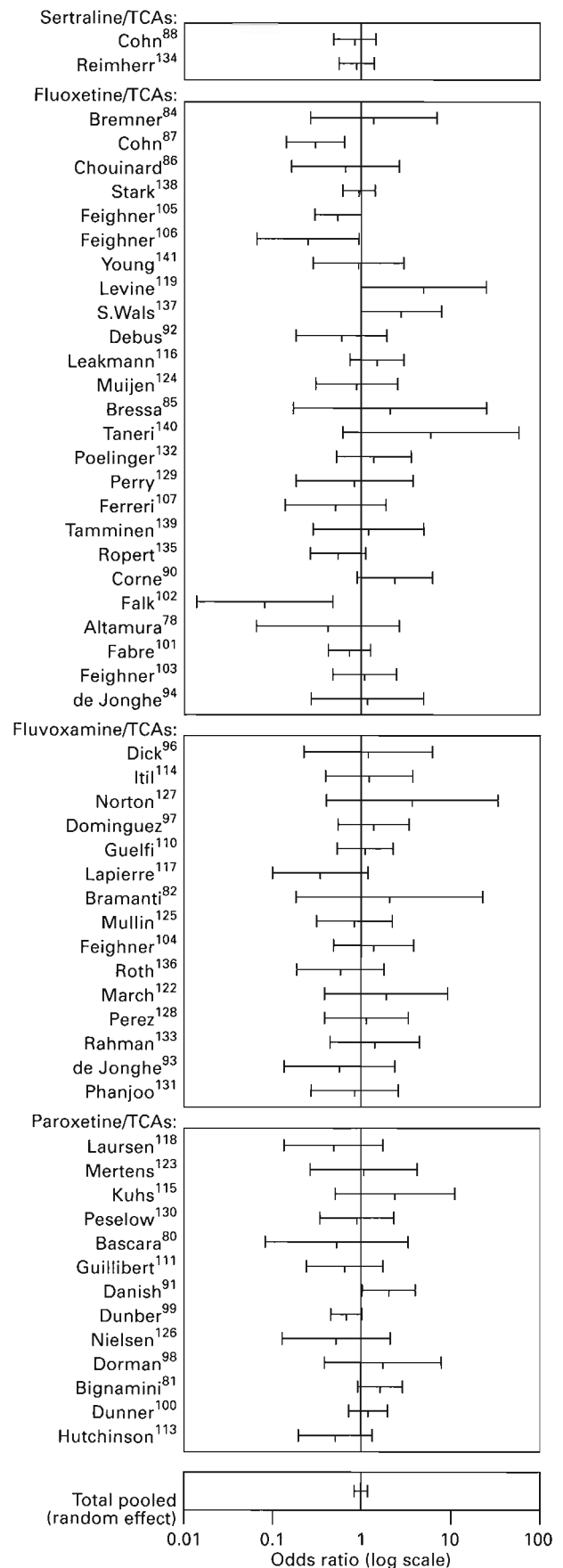
D.8 Acceptability Patient acceptability is an important element in treatment effectiveness.³⁷ Drop-out is a useful proxy for patient acceptability.¹⁴³ Drop-out is common in patients taking antidepressant medication, with rates of 22–32% reported in the primary care trials (See Appendix II). Acceptability of the SSRIs and tricyclic antidepressants was assessed by comparing total drop-out from each arm of the 58 trials where this was

Table D.2 Drop-out from trials of SSRIs and TCAs and related antidepressants.

	Drop-out (%) SSRIs	Drop-out (%) TCAs & related	Odds ratio	95% CI
Total drop-outs	32.3	33.2	0.950	0.816–1.107
Drop-out due to side-effects	15.4	18.80	0.805	0.648–1.001
Drop-out due to inefficacy	7.0	6.80	1.022	0.801–1.304

Source: Song *et al.*¹⁴²

Figure 3 Pooled odds ratios and drop-out from comparative SSRI trials (with 95% confidence intervals).



Source: Song *et al.*¹⁴² Reproduced with permission.

Table D.3 Death rates by poisoning from antidepressant either taken alone (low) or in combination with other substances (high) by class of antidepressant (1990 data).

Total units of treatment		Total deaths by class		Death rates per 1000 person years of treatment	
		low	high	low	high
All deaths	7 363 995	306	448	0.542	0.793
SSRIs	260 910	0	0	0	0
Older TCAs	5 859 897	298	432	0.663	0.961
Newer TCAs and related	1 243 188	8	16	0.084	0.168

Source: OPCS¹⁴⁴, Prescriptions Pricing Authority.

reported. There was a total of 5518 patients included in the analysis (2817 received SSRIs and 2701 received tricyclic or related compounds). There is no difference in drop-out rates between patients in the SSRI group of antidepressants and the tricyclic or related antidepressants (odds ratio 0.95; 95% CI: 0.816, 1.107). See Table D.2 and Figure 3.¹⁴²

D.9 Safety in overdose Older tricyclic antidepressants are more toxic in overdose (when measured as deaths per thousand years of treatment) than more recent tricyclic and related antidepressants and the SSRIs (see Table D.3).

D.10 Deaths from poisoning by antidepressant, or by solid or liquid substances in which antidepressants were listed among those substances ingested (though not necessarily causing death), in England and Wales in 1990 are shown by major class of antidepressant in Table D.3.¹⁴⁴ These deaths represent around 21% of all poisonings, and 7% of all suicides and undetermined deaths in 1990 (the most recent year for which this data are currently available).¹⁴⁴ By comparison, paracetamol was the single attributed cause in around 10% of fatal poisonings in England and Wales, either accidentally or purposely inflicted, in 1990.¹⁴⁴

D.11 The SSRIs are not completely without risk in overdose; one death as a result of fluvoxamine poisoning¹⁴⁵ and another as a result of fluoxetine poisoning¹⁴⁶ have been recorded. A more comprehensive picture of the side-effects and toxicity of newer drugs will only be obtained after several years of use. An early SSRI, zimelidine, was withdrawn when it was found to be associated with dangerous side-effects.⁶⁴

D.12 The SSRIs may well have a place in the treatment of depression for particular subgroups of patients in whom other treatments are contra-indicated or have failed. However it is unclear what impact a strategy of widespread use of SSRIs for routine first-line treatment of depression would have on actual suicide rates, as patients may seek alternative readily available means.^{147,148} There are also a number of less expensive tricyclic and related antidepressants which are relatively safe in overdose.

D.13 It is estimated that the NHS drug budget for antidepressants in England would increase by over £100m per year if SSRIs were substituted for the older tricyclics. In addition, there are indications that their use may be associated with increased use of additional drug therapy for insomnia and anxiety (sedatives and anxiolytics). On the basis of this evidence the increasing use of the SSRIs should be carefully monitored.

E. NON-DRUG TREATMENTS

A range of non-drug therapies such as cognitive therapy, psychotherapy, social work support and counselling is used for the treatment of major depression. Cognitive therapy has been shown to be as effective as 'treatment as usual' in primary care. Counselling is increasingly available in primary care, but requires evaluation as an intervention in depression.

E.1 A range of non-drug treatments is used in primary care settings. These include cognitive therapy, counselling, social work support, and interpersonal psychotherapy.

E.2 There have been six trials (see Appendix II) that have examined the effectiveness of non-drug treatments for depression in primary care, compared with some form of the treatment usually given by the GP.⁵⁶⁻⁶¹

E.3 Cognitive therapy has been shown to produce a more rapid improvement when compared with 'treatment as usual'.⁵⁷⁻⁵⁹ Though because a placebo group is rarely included, it is not clear how much improvement a 'treatment as usual' group demonstrates. However, this difference was not sustained beyond 16 weeks after commencement of therapy in one study,⁵⁶ and 12 weeks after completion of therapy in another.⁵⁷ Cognitive therapy, alone or in combination with other treatment, may reduce relapse¹⁴⁹ (see E.8).

E.4 Cognitive therapy in primary care produces a parallel reduction in anxiety where it accompanies depression.⁵⁹

E.5 Drop-out among those receiving cognitive therapy ranged between 20–38% in the primary care trials,⁵⁶⁻⁵⁹ which is of the same order as in the drug trials. Drop-out for health visitor counselling was 9%,⁶⁰ and 15% for social work support.⁶¹

E.6 A trial of social work support in women indicated a significant benefit for those with an acute episode of

depression on top of a long-standing depression when compared with treatment as usual.⁶¹ A trial comparing counselling by health visitors with 'treatment as usual' found twice the rate of recovery in women with post-natal depression who received counselling.⁶⁰

E.7 Non-drug treatments have been compared with drug treatments in large outpatient trials.^{65,66} Drug treatments appear to be the most effective in *major depression*, but cognitive therapy and interpersonal psychotherapy are also effective, especially in less severe episodes. However these comparisons are limited by the narrow measures of outcome and the limited length of follow-up.

E.8 The follow-up of a large US collaborative trial in outpatients indicates the possibility that cognitive therapy may reduce relapse and recurrence;¹⁵⁰ however these findings were not adequately controlled and this requires more systematic evaluation. Evidence from an outpatient trial suggests that there may be a slight additive value from cognitive therapy and drug therapy combined,¹⁵¹ but the additional benefits appeared small and have not been replicated in the primary care setting.

E.9 Around one third of practices employ a whole time therapist for counselling but there is considerable variation in their professional backgrounds and qualifications.¹⁵²

E.10 No reports of evaluation of counselling in depression were identified. The evidence for the effectiveness of employing counsellors in primary care for patients with psychological problems is ambiguous.¹⁵³⁻¹⁵⁷ Measuring the effectiveness of interventions in this area is problematic, especially considering the different skills and approaches utilised and the need to develop a range of outcome measures.

E.11 Non-drug therapies are often popular with patients,¹⁵⁸ and counsellors could potentially complement the work of GPs, but this strategy requires thorough evaluation. The cost of various non-drug treatment strategies for depression are given in Table E.1.

Table E.1 *The cost of non-drug treatment (1992/93 prices)*

- The cost to GPs of referral to a psychiatrist is around £90 (range £40-140) for a first visit and £40 (range £20-70) for subsequent visits.
- The cost of a domiciliary visit by a psychiatrist is around £100 (range £60-180).
- The cost of employing a counsellor in the GP setting varies from £15-35 per hour depending upon employment status and level of supervision, training and responsibility.
- The cost to GPs of referral for psychotherapy is around £170 for a first visit (ranging from £110-250) and £80 for follow-on visits (range £50-110).

Source: Trent RHA¹⁵⁹, Ball¹⁶⁰

F. RECOMMENDATIONS FOR DECISION-MAKERS

Clinical guidelines for the detection and management of depression in primary care should be developed with the participation of a wide range of health service organisations, professions, voluntary groups and consumers.

F.1 *Clinical guidelines* for depressed people will be influenced by the available services locally, but could include:

- (i) criteria for detection/recognition of *major depression* in primary care, based upon a reliable diagnostic classification such as DSMIII-R.
- (ii) clear guidance on appropriate treatment packages, including criteria for non-drug therapies and the prescription of different drug treatments. The guidelines may include a *limited list* of drugs to ensure cost-effectiveness whilst taking into account special needs.
- (iii) FHSAs and purchasing authorities should consider allocating resources to fund suitably qualified cognitive therapists to improve the range of effective treatment options.
- (iv) guidelines should also consider strategies for improving compliance with treatments.
- (v) Given the multifactorial causation of depression, FHSAs, purchasing authorities and local authorities should identify ways in which co-ordinated interventions in the health and social spheres can be developed to help depressed individuals, and populations with high rates of depression.

G. RESEARCH RECOMMENDATIONS

G.1 Research is required to examine the extent to which training packages for the primary health care team can improve the recognition and management of depression.

G.2 Further research is required to evaluate management of depression in population subgroups, such as the elderly and young.

G.3 Further research is required to evaluate the effectiveness of non-drug therapies, in particular counselling, and to examine their role within the broad spectrum of primary care interventions.

G.4 Research over a longer time span is required to identify the effect, if any, of treatments upon the natural history of depression in primary care.

G.5 Research is required to identify more patient-centred outcome measures for use in both evaluation and monitoring of treatments.

G.6 The management and audit of services for depressed people requires research to evaluate effective models for the delivery of high quality care which is responsive to the needs of the patient.

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APPENDIX I

DSMIII-R criteria for major depression⁶

- A. At least five of the following symptoms have been present during the same two week period and represent a change from previous functioning; at least one of the symptoms is either (1) *depressed mood*, or (2) *loss of interest or pleasure*. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucinations, incoherence, or marked loosening of associations.)
- (1) Depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day, as indicated either by subjective account or observation by others.
 - (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time).
 - (3) Significant weight loss or weight gain when not dieting (eg more than 5% of body weight in a month), or decrease or increase in appetite nearly every day (in children consider failure to make expected weight gains).
 - (4) Insomnia or hypersomnia nearly every day.
 - (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
 - (6) Fatigue or loss of energy nearly every day.
 - (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 - (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
 - (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. (1) It cannot be established that an organic factor initiated and maintained the disturbance;
 (2) The disturbance is not a normal reaction to the death of a loved one (uncomplicated bereavement).
Note: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by major depression.
- C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (ie before the mood symptoms developed or after they have remitted).
- D. Not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not superimposed on schizophrenia.

APPENDIX II

Author	Intervention	Patient Characteristics	Main Outcome Measures	Main Results/Comments
Blackburn ⁵⁹	Cognitive therapy = 13 Tricyclic 150 mg/day or equivalent = 12 Combination of both (Numbers entered into trial) = 14 Treatments lasted for 12 weeks	Aged 18–65 Both sexes (83% women) RDC major depression BDI >14 Mean initial HAMD = 19.0	BDI HAMD Irritability, depression and anxiety scale	38% drop-out during treatment, similar in all groups. 77% reduction in HAMD in cognitive therapy group, 16% in drug group (significant), combination therapy resulted in no additional improvement. * response in drug group less than in placebo group in other trials.
Blashki ⁴⁴	Amitriptyline 75 mg/day = 13 Amitriptyline 150 mg/day = 14 Amylobarbitone 150 mg/day = 16 Placebo = 18 (Numbers completing treatment) Treatments lasted for 4 weeks	Aged over 15 Women only Non-standard case definition Mean initial HAMD = 17.4	HAMD Zung rating scale Clinical rating of depression Taylor manifest anxiety scale Clinical rating of anxiety Side-effect check-list	22% drop-out, similar in all groups. 84.2% reduction in HAMD in amitriptyline 150 mg/day group, 63.4% reduction in amitriptyline 75 mg/day group and 39.7% reduction in placebo group. Drug-placebo difference only significant for amitriptyline 150 mg/day group.

Author	Intervention	Patient Characteristics	Main Outcome Measures	Main Results/Comments
Corney ⁶¹	Treatment as usual = 39 Social Work = 41 Counselling = 41 (Numbers entered into trial) Treatment lasted for 6 months	Aged 18–45 Women only GP diagnosed “acute” or “acute-on-chronic” depression	Goldberg Standardised Psychiatric Interview. Standardised Social Adjustment Scale.	15% of social worker group refused to see social worker. No significant difference in outcome between treatment groups. Retrospective analysis identified a group of women with acute-on-chronic depression and marital difficulties with a significantly better outcome in the social worker group.
Gomez ⁶²	Amitriptyline 75 mg/day plus perphenazine 6 mg/day = 68 Placebo = 73 (Numbers completing treatment) Treatment lasted for 6 weeks	Age not specified, at least 20–61 Both sexes (70% women) Non-standard case definition	Non-standard symptom check-list	Drug treatment produced significantly more improvement in both depression and anxiety than placebo. * Drop-out not reported
Holden ⁶⁰	Counselling by health visitor = 26 Routine health visitor care = 24 (Numbers completing treatment) Treatment lasted for 8 weeks	Post-natal women RDC depression (68% major depression)	Goldberg Standardised Psychiatric Interview. Edinburgh Postnatal Depression Scale.	9% drop-out. 69% of counselled group recovered compared to 38% of usual care group (significant).
Hollyman ⁵³	Amitriptyline 150 mg/day = 90 Placebo = 88 (Numbers entered into trial) Treatment lasted for 6 weeks	Aged 18–64 Both sexes (83% women) RDC major, minor and intermittent depression Mean initial HAMD = 14.8	HAMD Raskin Three Area Depression Scale. Clinical interview for depression. Global rating of severity.	31% drop-out in amitriptyline group and 27% in placebo group. 63% reduction in HAMD in amitriptyline group and 41% reduction in placebo group (significant). Drug-placebo difference only occurred in definite/probable major depression and HAMD > 13.
Murphy ⁵⁵	Mianserin 40 mg/day = 35 Imipramine 100 mg/day = 34 Placebo = 33 (Numbers entered into trial) Treatments lasted for 6 weeks	Aged 13–70 Both sexes Non-standard case definition	Non-standard physician and patient ratings. Side-effect inventory.	17% drop-out in mianserin group, 24% in imipramine group and 15% in placebo group. Significantly greater improvement in symptom scores in mianserin and imipramine groups compared to placebo. No significant drug-drug difference.
Porter ⁵⁴	Imipramine 75–150 mg/day = 26 Placebo = 29 (Numbers completing treatment) Treatment lasted for 3 weeks	Aged over 15 Both sexes (83% female) Non-standard case definition	Clinical ratings of depression, anxiety, agitation, hypochondria and retardation.	33% of subjects removed from trial or defaulted on treatment. No significant drug-placebo difference although both groups improved considerably.
Ross ⁵⁸	Individual cognitive therapy = 21 Group cognitive therapy = 9 3-month usual treatment followed by cognitive therapy = 21 (Numbers entered into trial) Treatments lasted for 3 months	Age not specified Both sexes (63% women) RDC major depression BDI > 14	Montgomery-Asberg Depression Scale. BDI.	37% drop-out from cognitive therapy. 64% reduction in BDI in cognitive therapy group compared to 13% reduction in usual treatment group (significant). No difference in outcome between individual and group cognitive therapy groups. * Unusual control group
Scott ⁵⁶	Routine GP care = 30 Amitriptyline 150 mg/day from consultant psychiatrist = 31 Social work counselling = 30 Cognitive therapy = 30 (Numbers entered into trial) Treatments lasted for up to 16 weeks	Aged 18–65 Both sexes (61% women) DSM-III major depression Mean initial HAMD = 18.0	HAMD. Patient rating of treatment acceptability.	16% of amitriptyline group refused to see psychiatrist. 21% of cognitive therapy group dropped out during treatment. Amitriptyline group showed greatest reduction in HAMD at four weeks (not significant when adjusted for baseline differences). At 16 weeks no significant difference between treatment groups in improvement in HAMD. Social work counselling most positively rated by patients.
Teasdale ⁵⁷	Cognitive therapy = 24 Usual GP care = 20 (Numbers entered into trial) Treatment lasted around 16 weeks	Aged 18–60 Both sexes (94% women) RDC major depression HAMD > 14 BDI > 20 Mean initial HAMD = 18.5	HAMD. BDI. Montgomery-Asberg Depression Scale.	29% drop-out in cognitive therapy group and 15% drop-out in usual care group. 79% reduction in HAMD in cognitive therapy group and 17% reduction in usual care group (significant). Cognitive therapy group later deteriorated and usual care group improved so that there was no difference between groups 3 months after completion of treatment.
Thompson ⁴⁶	Dothiepin 75 mg/day = 25 Placebo = 27 (Numbers entered into trial) Treatment lasted for 4 weeks	Age not specified Both sexes (88% women) GP-diagnosed depressives (73% RDC definite or probable major depression) Mean initial HAMD = 17.4	HAMD. Kellner self-rating test. Global severity. Side-effect profile.	56% drop-out in dothiepin group and 33% drop-out in placebo group. 62.5% reduction in HAMD in dothiepin group and 45.3% reduction in placebo group (non-significant).

Author	Intervention	Patient Characteristics	Main Outcome Measures	Main Results/Comments
Thomson ⁴⁵	Amitriptyline 150 mg/day = 31 L-Tryptophan 3 g/day = 29 Combination of both = 27 Placebo = 28 (Numbers entered into trial) Treatments lasted for 12 weeks	Aged 18–65 Both sexes (78% women) 94% RDC major depression HAMD >12 Mean HAMD = 21.0	HAMD. Global scale. Patient visual analogue scale. Side-effect checklist.	32% drop-out in amitriptyline group and 46% drop-out in placebo group. 72% reduction in HAMD in amitriptyline group and 59% reduction in placebo group (significant). * L-Tryptophan since withdrawn.

Key BDI Beck Depression Inventory
HAMD Hamilton Depression Rating Scale
RDC Research Diagnostic Criteria
* Comments

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