

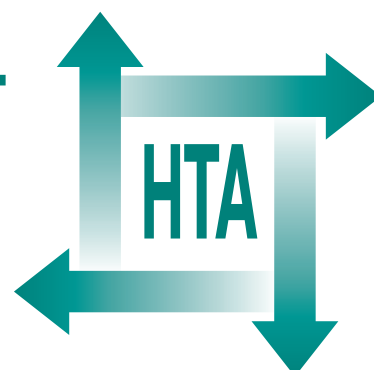
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine

R Peveler, T Kendrick, M Buxton,
L Longworth, D Baldwin, M Moore,
J Chatwin, J Goddard, A Thornett,
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May 2005

**Health Technology Assessment
NHS R&D HTA Programme**





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Abstract

A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine

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Objective: To determine the relative cost-effectiveness of three classes of antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and the modified TCA lofepramine, as first choice treatments for depression in primary care.

Design: Open, pragmatic, controlled trial with three randomised arms and one preference arm. Patients were followed up for 12 months.

Setting: UK primary care: 73 practices in urban and rural areas in England.

Participants: Patients with a new episode of depressive illness according to GP diagnosis.

Interventions: Patients were randomised to receive a TCA (amitriptyline, dothiepin or imipramine), an SSRI (fluoxetine, sertraline or paroxetine) or lofepramine. Patients or GPs were able to choose an alternative treatment if preferred.

Main outcome measures: At baseline the Clinical Interview Schedule, Revised (CIS-R PROQSY computerised version) was administered to establish symptom profiles. Outcome measures over the 12-month follow-up included the Hospital Anxiety and Depression Scale self-rating of depression (HAD-D), CIS-R, EuroQol (EQ-5D) for quality of life, Short Form (SF-36) for generic health status, and patient and practice records of use of health and social services. The primary effectiveness outcome was the number of depression-free weeks (HAD-D less than 8, with interpolation of intervening values) and the primary cost outcome total direct NHS costs. Quality-adjusted life-years (QALYs) were used as the outcome measure in a secondary analysis. Incremental cost-effectiveness ratios and cost-effectiveness acceptability curves were computed. Estimates were bootstrapped with 5000 replications.

Results: In total, 327 patients were randomised. Follow-up rates were 78% at 3 months and 52% at

1 year. Linear regression analysis revealed no significant differences between groups in number of depression-free weeks when adjusted for baseline HAD-D. A higher proportion of patients randomised to TCAs entered the preference arm than those allocated to the other choices. Switching to another class of antidepressant in the first few weeks of treatment occurred significantly more often in the lofepramine arm and less in the preference arm. There were no significant differences between arms in mean cost per depression-free week. For values placed on an additional QALY of over £5000, treatment with SSRIs was likely to be the most cost-effective strategy. TCAs were the least likely to be cost-effective as first choice of antidepressant for most values of a depression-free week or QALY respectively, but these differences were relatively modest.

Conclusions: When comparing the different treatment options, no significant differences were found in outcomes or costs within the sample, but when outcomes and costs were analysed together, the resulting cost-effectiveness acceptability curves suggested that SSRIs were likely to be the most cost-effective option, although the probability of this did not rise above 0.6. Choosing lofepramine is likely to lead to a greater proportion of patients switching treatment in the first few weeks. Further research is still needed on the management of depressive illness in primary care. This should address areas such as the optimum severity threshold at which medication should be used; the feasibility and effectiveness of adopting structured depression management programmes in the UK context; the importance of factors such as physical co-morbidity and recent life events in GPs' prescribing decisions; alternative ways of collecting data; and the factors that give rise to many patients being reluctant to accept medication and discontinue treatment early.



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List of abbreviations

A&E	accident and emergency	KW	Kruskall–Wallis
AHEAD	Assessing Health Economics of Antidepressants	LOF	lofepramine
ANOVA	analysis of variance	LREC	local research ethics committee
BNF	British National Formulary	MAICER	maximum acceptable incremental cost-effectiveness ratio
CBT	cognitive behaviour therapy	MAR	missing at random
CCOHTA	Canadian Coordinating Office for Health Technology Assessment	MNAR	missing not at random
CEAC	cost-effectiveness acceptability curve	MRC	Medical Research Council
CI	confidence interval	MREC	multicentre research ethics committee
CIS-R	Clinical Interview Schedule – Revised	NCCHTA	National Coordinating Centre for Health Technology Assessment
DFW	depression-free week	NCR	no carbon required
EQ-5D	EuroQol 5 Dimensions	NICE	National Institute for Health and Clinical Excellence
HAD-A	Hospital Anxiety and Depression Scale – Anxiety subscale	OPCS	Office of Population Censuses and Surveys
HAD-D	Hospital Anxiety and Depression Scale – Depression subscale	PST	problem-solving therapy
HADS	Hospital Anxiety and Depression Scale	QALY	quality-adjusted life-years
HDP	Hampshire Depression Project	RCT	randomised controlled trial
HDRS	Hamilton Depression Rating Scale	R&D	research and development
HSCL	Hopkins Symptom Checklist	SD	standard deviation
ICD	International Classification of Diseases	SF-36	Short Form 36
ICER	incremental cost-effectiveness ratio	SNRI	serotonin and noradrenaline reuptake inhibitor
ITT	intention to treat	SSRI	selective serotonin reuptake inhibitor
		TCA	tricyclic antidepressant
		UHSS	Use of Health and Social Services

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Objectives

The main aim of this study was to determine the relative cost-effectiveness of three classes of antidepressant: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and the TCA-related antidepressant lofepramine, as first choice treatments for depression in primary care.

Methods

Design

The study was an open, pragmatic, controlled trial with three randomised arms and one preference arm. Patients were followed up for a total of 12 months.

Setting

The study took place in a UK primary care setting: 73 practices in urban and rural areas in Hampshire, Wiltshire, Dorset, Sussex and Surrey agreed initially to take part. Patients were referred by 87 GPs from 55 practices.

Participants

Patients with a new episode of depressive illness according to GP diagnosis were assessed. In total, 388 patients were referred to the study team.

Interventions

Patients were randomised to receive a TCA (amitriptyline dothiepin or imipramine), an SSRI (fluoxetine, sertraline or paroxetine) or lofepramine. Standardised recommendations about dose and dose escalation based on the British National Formulary were issued to GPs. Patients or GPs were able to choose an alternative treatment if preferred.

Main outcome measures

At baseline the Clinical Interview Schedule, Revised (CIS-R PROQSY computerised version) was administered to establish symptom profiles. Outcome measures over the 12-month follow-up included the Hospital Anxiety and Depression Scale self-rating of depression (HAD-D), CIS-R, EuroQol 5 Dimensions for quality of life, Short Form 36 for

generic health status, and patient and practice records of use of health and social services. The primary effectiveness outcome was the number of depression-free weeks (HAD-D <8, with interpolation of intervening values) and the primary cost outcome total direct NHS costs. Quality-adjusted life-years (QALYs) were used as the outcome measure in a secondary analysis. Incremental cost-effectiveness ratios and cost-effectiveness acceptability curves were computed. Estimates were bootstrapped with 5000 replications.

Results

In total, 327 patients were randomised. Follow-up rates were 78% at 3 months and 52% at 1 year. Linear regression analysis revealed no significant differences between groups in number of depression-free weeks when adjusted for baseline HAD-D. A higher proportion of patients randomised to TCAs entered the preference arm than those allocated to the other choices. Switching to another class of antidepressant in the first few weeks of treatment occurred significantly more often in the lofepramine arm and less in the preference arm. There were no significant differences between arms in mean cost per depression-free week. For values placed on an additional QALY of over £5000, treatment with SSRIs was likely to be the most cost-effective strategy. TCAs were the least likely to be cost-effective as first choice of antidepressant for most values of a depression-free week or QALY, but these differences were relatively modest.

Conclusions

Given the low probability of significant differences in cost-effectiveness, the authors conclude that it is appropriate to base the first choice between these three classes of antidepressant in primary care on doctor and patient preferences. Adopting this policy may lead to less switching of medication subsequently. Choosing lofepramine is likely to lead to a greater proportion of patients switching treatment in the first few weeks.

Recommendations for research

Recruitment to trials in primary care remains a difficult problem to solve. The following strategies may be helpful and should be investigated further:

- financially rewarding recruitment to high-quality research studies (those funded by the partnership organisations, the MRC, NHS R&D, and AMRC charities), by giving practices points in the General Medical Services performance-related contract, which is to be revised in 2006.
- funding nurse time in the practices, as in the MRC GP research framework
- using practitioners with a track record of recruiting to other studies
- working extensively with practitioners and support staff in a smaller number of practices, rather than stretching resources thinly over a large number of practices
- building in a pilot phase to test recruitment, and including qualitative interviews with patients, especially those declining to take part in the trial

- keeping the inclusion and exclusion criteria as brief and clear as possible
- keeping the information sheet as short as possible, but in keeping with giving enough information
- IT support including better email links with practices, and a website with study information
- pop-up screens on practice computers to remind practitioners to consider referral of patients with the relevant conditions.

Further research is still needed to address other important questions surrounding the management of depressive illness in primary care. This should address areas such as the optimum severity threshold at which medication should be used; the feasibility and effectiveness of adopting structured management programmes in the UK context; the importance of factors such as physical co-morbidity and recent life events in GP's prescribing decisions; alternative ways of collecting data, for example using telephone follow-up or payment for data; and factors that give rise to many patients being reluctant to accept medication and discontinue treatment early.

Chapter I

Background

Introduction

Depressive illness is a major global public health problem, affecting up to 5% of the population in any one year, and it is associated with significant social and occupational disability.^{1,2} Because of the high prevalence and chronicity of depression, most episodes are managed in primary care,³ and antidepressant drugs are currently the most widely used form of treatment. As a result, antidepressant prescribing makes up a large and growing fraction of the total cost of primary care prescribing in the UK. There were 26.3 million prescriptions in 2002, up 8.2% on 24.3 million in 2001. The net ingredient cost was £381 million, up by 11.5% from the £342 million in 2001, mainly due to increased prescribing of citalopram, venlafaxine and mirtazepine.⁴

The development of new medicines including the selective serotonin reuptake inhibitors (SSRIs) has produced benefits in terms of better tolerability and safety, but at higher acquisition cost. SSRIs are now the most commonly prescribed class of antidepressant drugs, accounting for £55.5 million for the second quarter of 2001. SSRI prescribing has increased by 143% over the past 5 years, while total cost has risen by 66%.⁵ There is no evidence that SSRIs have greater efficacy than other antidepressant drugs. However, it is argued that the more expensive medicines may be cost-effective if their higher acquisition costs are offset by a reduction in other non-medication costs. Some of the SSRIs are now at the end of their patent life, and will become cheaper as a result.

Uncertainty over the cost-effectiveness of different types of antidepressant is only part of a wider field of enquiry into the most appropriate diagnostic and management procedures for depression in primary care. Psychological treatment is more expensive, but is often the preferred treatment of patients.⁶ Clinical guidelines are now in circulation⁷⁻¹⁰ that summarise available evidence about the best approach to management, and ideally they would indicate optimum initial treatment choice at lowest cost. However, for them to be able to do this, more evidence is needed about the relative costs and benefits of the available forms of treatment.

Existing guidelines are limited by the fact that much of the evidence on which their recommendations are based is derived from secondary care patient populations, and there are doubts about the extent to which such evidence can be generalised to primary care. Although there is some suggestive evidence concerning cost-effectiveness of antidepressants from modelling and meta-analysis, accurate information is difficult to obtain, requiring carefully designed experiments in settings that are as naturalistic as possible. No such studies have been conducted within NHS settings. The current study was therefore planned to provide much needed data to inform initial antidepressant choice on the basis of cost-effectiveness in NHS primary care.

In this chapter, the context of the clinical and health economic questions will be described, and the rationale for the design of the study will be presented.

Epidemiology and clinical features of depressive disorders in primary care

The Office of Population Censuses and Surveys (OPCS) community survey of Great Britain found a weekly prevalence of 1.7% for depressive disorders and 7.1% for mixed anxiety and depressive disorder.¹¹ The prevalence is two to three times higher in women than in men.¹² Depression may be a short-term reaction to adverse life events, but is often associated with significant impairment of functioning.^{13,14} Depression and anxiety account for around 80 million working days lost each year in England.¹⁵

Around 5% of patients consulting in UK general practice are found on screening to have major depression, but a further 10% or so have mild depression with or without anxiety.¹⁶⁻¹⁸ In a US survey an estimated 22% of family practice attenders were found to be depressed, including around 13% with major depression and 2% with dysthymia.¹⁹ Most cases of depression detected and treated by GPs tend to be below the threshold for major depression.²⁰

More than 50% of patients identified will recover within 6–12 months. A poorer outcome is associated with greater initial severity, less social support and higher neuroticism scores on personality testing.^{21–23} In the long term more than half remain free of recurrence, although a significant minority follow a chronic or relapsing course, again associated with greater initial severity.^{24,25}

Patients present to GPs with a broad spectrum of severity and chronicity of depressive symptoms. Although they may present with a primary complaint of depressed mood, most present with physical complaints.²⁶ Management is based on the assumption that the depressive disorder underlies the physical problem.

Current approaches to management

A wide range of pharmacological and psychological treatments is used, for which the evidence base is developing, but several key questions remain unanswered.

Drug treatment

Who should receive treatment?

Recent guidelines for management are based on classification of depressive episodes according to the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) criteria.⁹

Antidepressant treatment is effective for major depression of moderate and greater severity, including depression associated with physical illness, and for dysthymia. In placebo-controlled trials in patients with major depression of at least moderate severity, the response rates in intention-to-treat (ITT) samples are around 50–65% on antidepressants, compared with around 25–30% in those receiving placebo. In dysthymia, a meta-analysis of randomised controlled trials (RCTs) showed similar overall response rates.²⁷

By contrast, antidepressants do not appear more effective than placebo in patients with acute milder depression. The evidence is somewhat limited, but a post hoc analysis of a placebo-controlled trial with amitriptyline suggests that there was no advantage over placebo in mild depression (as indicated by a score of ≤ 15 on the Hamilton Rating Scale for Depression).²⁸

It is suggested that antidepressant treatment should be the first line treatment both for major depression and for dysthymia. By contrast, those

with milder depression should be offered education and support and monitored for the development of major depression. Patients with persistent mild symptoms or with a history of major depression can also be offered treatment.

With which antidepressant, and at what dose?

Systematic reviews and meta-analyses suggest that different antidepressant drugs have similar overall efficacy for the majority of patients with major depression.²⁹ In particular, the three classes of antidepressant included in this study are thought to be similarly efficacious, at least in patients with moderate depression. In hospitalised patients, however, tricyclic antidepressants (TCAs) may be more effective than SSRIs; and in patients with severe depression, the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine may be more efficacious than SSRIs.⁹ There is more debate over the tolerability and safety of older TCAs (e.g. amitriptyline and imipramine) compared with the newer TCA lofepramine and the SSRIs.

The justification for viewing the two major groups, TCAs and SSRIs, as homogeneous classes is rational and rests on four features. They have distinct dosage schedules: TCAs have to be titrated up to a known therapeutic dose, whereas SSRIs can be started at a therapeutic dose. They have distinct side-effects: TCAs have a range of receptor-blocking actions, whereas SSRIs chiefly induce nausea and headache. They have distinct cost profiles: TCAs are much cheaper to prescribe than SSRIs. Finally, they have different toxicities: TCAs are associated with 4% of all suicides, but SSRIs have a much broader therapeutic index. The second generation antidepressants do not fall into a single class, having a wide range of chemical structures, pharmacological actions, toxicities, dosing schedules and adverse effects. Only one, lofepramine, is at all commonly prescribed in primary care. It has been identified as a possibly cost-effective alternative to the SSRIs as it has low toxicity in overdose and is said to have a lower burden of side-effects than the TCAs.

There is, however, little consensus about the merits of different classes of drug as the first line treatment. Although there have been many studies, few have been carried out in the primary care setting, and none has used a representative sample of depressed patients. Many studies have been commercially driven and underpowered. Meta analyses cannot overcome these limitations, but may be used to estimate differential efficacy and compliance under

relatively ideal prescribing conditions. Bearing in mind the pitfalls of extrapolation from such data to routine practice, the meta-analyses suggest that the SSRIs and TCAs are of roughly equal efficacy when the latter are given in full dose.^{30,31} This does not, however, necessarily indicate equal effectiveness in routine practice.

Current guidelines suggest treatment with TCAs at a dose of 125–150 mg daily, and note that if patients respond to a lower dose, the dose should still be increased into the target range.⁹ This view has been challenged by the observation that in primary care cohort studies patients are as likely to respond to 'less than recommended' as to 'adequate' doses of TCAs.^{32–34} A recent systematic review compared outcomes in adults treated for major depression with low-dose (75–100 mg) or standard-dose TCAs, and found that low-dose treatment was more effective than placebo treatment. Standard-dose treatment was no more effective than low-dose treatment, but was more likely to result in patient dropouts due to side-effects.³⁵ The repeated observation that TCAs are consistently prescribed in primary care at lower than recommended doses may thus be of little significance.³⁶

Because of their formulations, SSRIs are nearly always prescribed at doses proven to be efficacious, and are more likely than TCAs to be prescribed for longer periods.³⁷ This would appear to offer an advantage, but there is no direct evidence that patients prescribed SSRIs have a better overall outcome than patients taking TCAs.

For how long?

Depression is increasingly conceptualised as an episodic illness, requiring both short-term and long-term treatment. After starting antidepressant treatment, the symptoms of depression may reduce (response) and then cease (remission). Stable remission of 4–6 months is conventionally regarded as recovery. A worsening of symptoms before recovery is regarded as a relapse, whereas a return of symptoms following recovery is considered a recurrence (i.e. a new episode of illness). By convention, prevention of relapse is called continuation treatment, whereas prevention of recurrence is called maintenance (or prophylactic) treatment.

Approximately one-third of patients will relapse, following earlier successful acute treatment.^{38,39} Meta-analysis of controlled studies in which patients with major depression were treated with antidepressants for 2–6 months following

remission found a reduction in relapse rate of 50% with active treatment.⁴⁰ Older guidelines recommended continuation treatment for 6 months following response, or for 4 months following complete remission.⁴¹ The British Association of Psychopharmacology (BAP) guidelines recommend that antidepressants should be continued for a minimum of 6 months after remission of depression (and for 12 months in the elderly), at the same dose as in acute treatment.⁹

Maintenance antidepressant treatment reduces the recurrence rate in patients who have had three or more episodes of major depression in the previous 5 years, or more than five episodes in their lifetime.⁹ The BAP guidelines make recommendations on this evidence, but most of the patients included in maintenance treatment studies are seen in secondary care settings, whereas the long-term outcome in primary care depressed patients (and therefore the value or otherwise of long-term treatment) is unknown.

Treatment of residual symptoms

Patients who respond to treatment, but who have 'residual' symptoms (i.e. persisting mild symptoms and/or social or occupational impairment) are at greater risk of relapse, and longer periods of treatment following complete remission are appropriate in these patients.⁷ Newer guidelines reflect these observations and recommend continuation treatment for a minimum of 6 months following remission, and longer in those with residual symptoms.⁹

GP non-adherence to guidelines for prescribing

Most GPs do not restrict prescribing to the full depressive syndromes on which RCTs have been carried out. Thus, the clinical trials do not represent the reality of prescribing in primary care and the relative effectiveness in this setting cannot be assessed from available studies.

Few patients in primary care are prescribed antidepressant treatment of adequate duration as defined by the guidelines.⁴² The reason for this, and the lack of change despite an intensive educational initiative, has been the subject of much debate.^{8,43,44} As described above, a recent meta-analysis suggested that lower doses of TCAs, at least down to the equivalent of 75 mg of amitriptyline per day, are effective in the treatment of major depression.³⁵

Many patients think that antidepressants are addictive, do not like taking higher doses and tend to want to stop treatment as soon as they

start to feel better.^{45,46} In primary care arrangements for routine follow-up, audit and monitoring of treated patients are not well established. Quality control of care is therefore difficult to establish even if adequate treatment has been initiated. Disease registers and special chronic disease clinics may represent a partial solution to this problem, but may be constrained by reimbursement systems.⁴⁷

Patient non-adherence

As in most chronic disease management, patient non-adherence limits the benefits from all classes of antidepressant. Differences in side-effects between classes are only one of several possible reasons for this. Song and colleagues,³⁰ taking all dropouts from clinical trials, found no significant advantage for the SSRIs, but Pande and Saylor⁴⁸ and Montgomery and colleagues,²³ taking a subgroup of those discontinuing owing to side-effects, did find an advantage. The advantage in dropout rates for SSRIs holds only against the older compounds (amitriptyline and imipramine) and not the newer TCAs (dothiepin, nortriptyline and clomipramine) or the 'heterocyclics' (mianserin, trazodone, deipramine and maprotiline).³¹ The largest absolute difference in reported discontinuation rates between TCAs and SSRIs is 2.8%,³⁴ which means that the number of patients who need to be treated to prevent one discontinuation is 38.⁴⁹ However, evidence from these trials may not be directly applicable to clinical practice in primary care, as trial populations are often selected for narrowly defined levels of severity of depression and the absence of co-morbid conditions such as alcohol use, which might make the SSRIs a more attractive option. A study of the ratio of discontinuations to inceptions of treatment in a naturalistic study of 13,619 inceptions in routine general practice found an 11% difference (22% versus 33%) in favour of the SSRIs, and the reported perceptions of the GPs studied suggested that tolerability rather than lack of efficacy explained most of this difference.⁵⁰ Similarly, Thompson and colleagues⁵¹ were able to show a 15% advantage in adherence for fluoxetine when compared with dothiepin in a primary care population. A recent systematic review and meta-analysis of the efficacy and tolerability of SSRIs compared with TCAs for the treatment of depression in primary care found that significantly more patients receiving a TCA withdrew from treatment. However, the evidence was sparse and of variable quality.⁵²

Whatever the true difference between classes, adherence is only an intermediate variable between efficacy and effectiveness, rather than an

end in itself. Previous studies which have used adherence as part of cost-effectiveness models have assumed that effectiveness is equal between classes because for the most part, efficacy appears equal. However, this is not necessarily true. The only valid method to assess cost-effectiveness is to measure it directly.

Psychological treatments

Efficacy of psychological treatments

Certain psychological treatments have proven efficacy in the acute treatment of patients with depression and are a possible alternative to drug treatment. Controlled treatment studies have demonstrated that cognitive behaviour therapy (CBT) and behaviour therapy,⁵³ interpersonal therapy⁵⁴ and problem-solving therapy (PST)⁵⁵ are all efficacious in short-term treatment in major depression. In patients with mild to moderate severity of depression, specific psychological treatments and antidepressants are similarly efficacious, but there is no clear advantage for combining the two approaches.⁹

Cognitive behaviour therapy

Cognitive behaviour therapy, or CBT, is a manual-based therapy given by specially trained therapists working with depressed patients to identify and combat 'automatic negative thoughts', and involves patients in keeping diaries of symptoms, thoughts and behaviours as 'homework' between therapy sessions.

A meta-analysis of 48 RCTs of cognitive therapy for mild to moderate depression, including patients with borderline major depression and dysthymia, found that it had a beneficial effect on symptoms compared with waiting-list or placebo controls (average patient 29% better, effect size 0.82), which was equivalent to that of behaviour therapy, superior to antidepressants (average patient 15% better, effect size 0.38) and superior to other psychological therapies, including psychodynamic, interpersonal, non-directive, supportive and relaxation therapies, and alternative bibliotherapy (average patient 10% better, effect size 0.24).⁵⁶

CBT is relatively expensive, however, as treatment typically involves 15–20 1-hour sessions with a trained therapist. The availability of CBT therapists in the UK is limited, leading to typical waiting times for treatment of several months.

Problem-solving therapy

PST is a brief (five- or six-session) therapy that involves identifying specific important problems in

the patient's life, and generating and selecting solutions for the patient to implement between therapy sessions. It is a manual-based therapy involving a specific training that should include the treatment of five patients under supervision.

General practice-based trials in patients with probable major depression have found PST to be as effective as amitriptyline⁵⁵ and the SSRIs fluvoxamine or paroxetine.⁵⁷ The combination of PST with SSRIs was no more effective than either treatment alone.

An RCT carried out in nine centres in five European countries, involving 452 patients identified through community surveys with mild to moderate depressive or adjustment disorders (including 14% with dysthymia), found both PST and group psychoeducation to be more effective than no intervention in terms of recovery [proportion depressed at 6 months 17% less with PST, number needed to treat=6, and 14% less for group psychoeducation, number needed to treat=7].⁵⁸

A recent US trial of PST versus paroxetine treatment versus placebo plus non-specific clinical management found, among adult patients with dysthymia, that the remission rate at 11 weeks was significantly higher with PST (57%) than with placebo drug treatment (44%), although lower than the rate for paroxetine treatment (80%).⁵⁹ The results for patients aged 60 years or over were equivocal; PST was no better than placebo plus supportive care in terms of reducing depressive symptoms at 11 weeks in dysthymia, although symptom levels seemed to fall more quickly in the PST-treated groups.⁶⁰

Counselling

Counselling includes addressing and resolving specific problems, making decisions, working through feelings and inner conflict, and improving relationships with others. Counsellors are now widespread in UK general practice, and counselling is relatively cheap as it typically involves only around six sessions.

The comparative efficacy of counselling and routine GP care in relieving depressive symptoms in primary care patients has been examined in a number of RCTs.⁶¹⁻⁶⁴ The earlier trials⁶¹⁻⁶³ could find little evidence for efficacy in the per protocol analysis, although a post hoc analysis in one study⁶³ suggested that outcomes were improved in severely depressed patients allocated to counselling, and one study with rather short-term follow-up and high rates of dropout indicated that

there were some advantages for counselling.⁶⁴ The results of a more recent RCT in general practices in Manchester and London indicated that both CBT and non-directive counselling were significantly superior to usual GP care, although there were no differences between the two psychological treatments.⁶⁵ By contrast, there was no advantage in relieving depressive symptoms or improving social function for psychodynamic counselling over standard GP care in a study conducted in Derbyshire.⁶⁶

A Cochrane systematic review of seven trials of primary care counselling identified a modest but significant improvement in symptoms of anxiety and depression in the short term (6 weeks to 4 months) compared with usual GP care [standardised mean difference -0.28, 95% confidence interval (CI) -0.43 to -0.13, $n = 772$, six trials], but no additional advantages in the long term (standardised mean difference -0.09, 95% CI -0.27 to 0.10, $n = 475$, four trials).⁶⁷ Patients were highly satisfied with counselling, and it appeared not to be more costly than GP care, although economic analyses were carried out in only four studies and the studies were probably underpowered to detect differences in costs.

Bibliotherapy

Bibliotherapy is based on CBT, and involves the patient taking home a standardised treatment in book form to work through more or less independently (books containing information only are not regarded as bibliotherapy). Intermittent contact by telephone is necessary to prevent patients giving up prematurely, and to monitor them for deterioration. It has been shown in a meta-analysis of six controlled trials to confer benefits in the short term in subjects with mild to moderate depression (mean effect size 0.82, 95% CI 0.50 to 1.15).⁶⁸ However, all of the studies analysed were small (fewer than 25 patients), lacked longer term follow-up and included patients who answered advertisements for recruitment rather than being referred by GPs.

A more recent systematic review of eight studies involving patients identified and referred by GPs with anxiety disorders, mixed anxiety and depression, and stress-related problems, found that the majority reported significant although modest advantages in outcome (mean effect size 0.41, 95% CI 0.09 to 0.72), but again several methodological limitations were identified.⁶⁹

Thus, although there is now considerable evidence for the effectiveness of psychological treatments,

there are very few data on longer term benefits or on cost-effectiveness.

Previous work on the cost-effectiveness of antidepressant drugs

As mentioned in the Introduction to this chapter, there have been no previous studies of cost-effectiveness of antidepressants in the NHS setting. A review of the existing published literature was conducted searching MEDLINE, the NHS Economics Evaluation Database and the Office of Health Economics Health Economics Evaluation Database. Search terms included 'lofepramine', 'tricyclic' and 'serotonin re-uptake inhibitors'. The results were restricted to publications also matching subject headings of 'economics', 'costs and cost analysis' and 'cost-benefit analysis' or 'cost-effectiveness' as a keyword. Abstracts of studies were reviewed, and studies comparing the costs and effects of treatment for depression using at least one TCA and at least one SSRI were selected (*Table 1*).

No published studies specifically designed to evaluate the cost-effectiveness of lofepramine were found. However, a number of economic evaluations comparing SSRIs and TCAs has been published. The majority of these use decision-analytic techniques and are based on secondary data.^{18,70-77} Only three evaluations collected resource-use and outcome data within the studies, of which two studies collected data prospectively alongside clinical trials.⁷⁸⁻⁸⁰

Of the evaluations using decision-analytic techniques to evaluate the cost-effectiveness of these medications in outpatients or primary care, the majority found in favour of SSRIs. An early study by Hatzianandreu and colleagues found that the SSRI sertraline produced additional quality-adjusted life-years (QALYs) at additional cost compared with the TCA dothiepin.⁷³ Revicki and colleagues found similar results in a study of the SSRI fluoxetine compared with the TCA imipramine.⁷⁰ Results from an analysis by Jonsson and Bebbington found the costs of SSRIs and TCAs to be similar, but also found that the cost per 'successfully treated' patient was lower in patients prescribed the SSRI paroxetine than in those prescribed imipramine.⁷² Another study using decision-analytic methods, by Nuijten and colleagues, found that the SSRI fluvoxamine was associated with a greater percentage of time free from depression at a slightly reduced cost

compared with TCAs.⁷¹ Doyle and colleagues used decision-analytic methods to compare the cost-effectiveness of the SNRI venlafaxine with SSRIs and TCAs for ten countries in both inpatient and outpatient settings. Their results also suggested that SSRIs dominated tricyclics in an inpatient setting as they produced improved outcome at no additional cost, or at a cost saving, for all ten countries. Their results for outpatient settings suggested that SSRIs dominated TCAs in eight countries, including the UK, but produced additional benefit at a cost in two countries.⁷⁴ Einarson and colleagues found that SSRIs dominated TCAs when compared in an outpatient setting, but that TCAs dominated SSRIs when compared in an inpatient setting.⁷⁶ Results from a study by the Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA) suggested that first line treatment (allowing for switching) with SSRIs produced a QALY gain at an additional cost compared with first line treatment with TCAs. This study also suggested that first line treatment with SSRIs was both cost saving and produced a QALY gain if compared with a treatment option of TCAs only.⁷⁷ One study was identified which suggested that TCAs may be more cost-effective than SSRIs. The study by Woods and Rizzo found the TCA imipramine to be more cost-effective than the SSRI paroxetine.¹⁸

All of these studies have used a large amount of secondary data to populate the decision-analytic models. The majority rely on judgements by expert panels to quantify parameters, particularly for resource-use estimates, which may be inaccurate and prone to bias. A large number of assumptions need to be imposed upon these models, and varying the assumptions can greatly affect the conclusions drawn. Woods and Rizzo¹⁸ used the structure of the model developed by Jonsson and Bebbington,⁷² but imposed a different set of assumptions. They found that the results from the model suggested that the TCA imipramine was more cost-effective than the SSRI paroxetine, whereas Jonsson and Bebbington concluded the opposite. This highlights the need for an economic evaluation based on primary data collection.

Only three previous studies have collected primary resource-use and outcome data⁷⁸⁻⁸⁰ and only one of these has produced estimates of cost-effectiveness.⁷⁸ The other two studies reported cost and outcomes data, but made no formal attempt to link them using cost-effectiveness ratios.

Forder and colleagues conducted a cost-effectiveness study to compare the SSRI sertraline

TABLE 1 Summary of literature search

Author	Type of evaluation	Framework of evaluation	Country	Comparison	Time horizon	Resource-use measures	Outcome measures	Authors' results
CCOHTA, 1997 ⁷⁷	Cost-utility analysis	Decision analytic model	Canadian analysis, which also contains data from other countries	Two analyses: (a) TCAs and SSRIs (allowing for switching in both arms) (b) TCAs and SSRIs (allowing for switching in TCA arm only)	3 months of acute treatment followed by 6 months of maintenance treatment	Estimated by clinical judgement	QALYs estimated using utility values from a published paper	(a) SSRIs show a QALY gain at an additional cost. ICER = \$2818 (b) SSRIs dominant compared with TCAs only
Doyle et al., 2001 ⁷⁴	Cost-effectiveness analysis	Decision-analytic model for ten countries	Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, USA and Venezuela	Venlafaxine with SSRIs and TCAs. Two analyses: (a) inpatient setting (b) outpatient setting	6 months	Estimated by expert panel from each country	Two measures: (i) 'success' defined as reduction in HDRS by 50% (estimates from published meta-analysis) (ii) number of symptom-free days	(a) Cost per success less for SSRIs than for TCAs in all ten countries. Cost per symptom-free day less for SSRIs than for TCAs in all ten countries. (b) Cost per success less for SSRIs than TCAs in eight of ten countries (not Italy and Poland). Cost per symptom-free day of SSRIs less than or equal to cost per symptom-free day of TCAs
Einarson et al., 1995 ⁷⁶	Cost-effectiveness analysis	Decision-analytic model	USA (also includes some Canadian data)	SSRIs, TCAs, venlafaxine. Two analyses: (a) inpatient setting (b) outpatient setting	1 year	Estimated by expert panel	Symptom-free days estimated by meta-analysis of published studies	(a) TCAs dominate SSRIs in an inpatient setting (b) SSRIs dominate TCAs in an outpatient setting
Forder et al., 1996 ⁷⁸	Cost-effectiveness analysis	Retrospective study	UK	Sertraline with TCAs	1 year	Patient notes, interviews with GPs and patients	'Successful treatment' defined by GPs retrospective opinion on improvement in symptoms	Sertraline more effective at slightly lower costs

continued

TABLE 1 Summary of literature search (cont'd)

Author	Type of evaluation	Framework of evaluation	Country	Comparison	Time horizon	Resource-use measures	Outcome measures	Authors' results
Hatziaudreu et al., 1994 ⁷³	Cost-utility analysis	Decision-analytic model	UK	Sertraline with dothiepin	Lifetime	Estimated by expert panel	QALYs. Utilities obtained by panel's valuation of four hypothetical health states.	Sertraline produces extra QALYs at an additional cost, (ICER = £2172, 1991 prices).
Hosak et al., 2000 ⁸⁰	Cost-consequences analysis	Prospective study alongside RCT	Czech Republic	Amitriptyline, citalopram and fluoxetine	6-months	Records obtained from physicians by questionnaires. Costs based on charges	Number of hospitalisation days measured prospectively	No significant differences in outcomes. No significant differences in total costs
Jonsson and Bebbington, 1994 ⁷²	Cost-effectiveness analysis	Decision-analytic model	UK (includes some data from other countries)	Paroxetine with imipramine	1 year	From literature and estimated by expert panel	'Successfully treated patient' defined as one who does not drop out from initial treatment. Based on pooled data from six RCTs	Cost per 'successfully treated patient' less for those taking paroxetine
Nuijten et al., 1998 ⁷¹	Cost-consequences analysis	Decision-analytic model	France (includes some data from other countries)	Fluoxetine with TCAs. Two analyses: (a) health insurer's perspective (b) societal perspective	18 months	Estimated by expert panel	Estimated time free from depression. Estimates based on published literature	Both analyses show the percentage of time free from depression to be greater for fluoxetine, and costs to be slightly less for fluoxetine
Revicki et al., 1997 ⁷⁰	Cost-utility analysis	Decision-analytic model	USA	Fluoxetine, imipramine, nefazodone and step approach (imipramine followed by nefazodone if initial treatment failed)	5, 10, 15 and 20 years and lifetime	Estimated by expert panel and from published literature	QALYs. Utilities derived from valuations of 11 hypothetical health states by a sample of patients	For the lifetime model fluoxetine produces extra QALYs at an additional cost compared with imipramine (\$6346 per QALY) and the imipramine step approach (\$5206 per QALY)
Simon et al., 1996 ⁷⁹	Cost-consequences analysis	Prospective study with RCT (USA)	USA	Fluoxetine with desipramine, fluoxetine with imipramine	6 months	Collected prospectively	Outcomes included HDRS, HSCL and SF-36. Measured prospectively	No significant differences in outcomes. No significant differences in total costs

continued

TABLE 1 Summary of literature search (cont'd)

Author	Type of evaluation	Framework of evaluation	Country	Comparison	Time horizon	Resource-use measures	Outcome measures	Authors' results
Simon et al., 1999 ⁸²	Cost-con-sequences analysis	Prospective study alongside RCT (USA)	USA	Fluoxetine with desipramine, fluoxetine with imipramine	2 years	Collected prospectively	Range of outcomes including HDRS, HSCL and SF-36. Measured prospectively	No significant differences in outcomes. No significant differences in total costs
Stewart, 1994 ⁷⁵	Cost-effectiveness analysis	Decision analytic model	UK (also includes non-UK data)	TCAs (imipramine, amitriptyline) with SSRIs (sertraline, paroxetine)	Up to 1 year	From literature and author's assumptions	Outcome measure is 'successfully treated patient' defined as one who does not drop out, where treatment is effective ("... succeeds in alleviating the level of depressive symptoms") and does not suffer a relapse. Estimates obtained from published literature	Cost per successfully treated patient slightly less for TCAs
Woods and Rizzo, 1997 ¹⁸	Cost-effectiveness analysis	Decision-analytic model	UK (includes some data from other countries)	Paroxetine with imipramine	Up to 3 years	From literature and estimated by expert panel	'Successfully treated patient' defined as one who does not drop out from initial treatment. Data obtained from published data	The Jonsson and Bebbington model is sensitive to changes in their assumptions. Under Woods and Rizzos preferred assumptions, imipramine is more cost-effective than paroxetine

with TCAs using a quasi-experimental retrospective design in a UK setting.⁷⁸ They recruited a subsample of GPs who participated in an earlier efficacy study of sertraline,⁸¹ and formed a control group by matching a group of TCA patients to the patients receiving sertraline. Resource-use data were collected for each patient over a 12-month period from the time they commenced their medication. GPs estimated the change in each patient's symptoms retrospectively and the treatment of a patient was categorised as 'successful' if GPs considered their symptoms to have improved over the study period. They found better outcomes in the sertraline group, measured in terms of successfully treated patients, than in the TCA group, and found that costs were lower in the sertraline group. Therefore, the study suggested that sertraline was the dominant treatment compared with TCAs. However, the retrospective nature of this study should be borne in mind when considering these results, as the non-randomisation of patients may introduce selection bias into the study, and the outcomes of patients were measured retrospectively and by GPs rather than by the patients or independent raters.

Simon and colleagues conducted an economic evaluation alongside a randomised trial in a naturalistic setting in the USA.⁷⁹ The study was designed to compare the costs and effects of the SSRI fluoxetine with the TCAs imipramine and desipramine. Altogether, 536 adults were randomly assigned to start treatment with one of the three choices. The dosage, medication changes and speciality referral were managed by the physician. Clinical and healthcare utilisation outcomes were examined after 1, 3 and 6 months. The analysis took the form of a cost-consequences study rather than a cost-effectiveness study, and there was no attempt to link costs with a measure of outcome. There was a non-significant advantage to fluoxetine in clinical outcome at 1 month, which had disappeared by 3 months and 6 months. They found no significant differences at 6 months using a range of outcome measures, including the Hamilton Depression Rating Scale (HDRS), the Hopkins Symptom Checklist (HSCL) and the mental health domain of the Short Form 36 (SF-36). They also found no significant differences in costs. Higher direct prescribing costs were balanced by fewer outpatient and inpatient costs. Details of results from a longer term (2-year) follow-up for this study have also been published, with similar conclusions.⁸²

The second prospective cost-consequences study was conducted alongside a randomised clinical trial by Hosak and colleagues in the Czech

Republic.⁸⁰ This compared the costs and effects of the TCA amitriptyline with the SSRIs citalopram and fluoxetine. The analysis was designed to be from the insurer's perspective and the measure of outcome used was 'days free from hospitalisation'. Resource-use information was collected by questionnaires completed by physicians and costs were based on hospital charges. The investigators found no significant differences in either costs or outcomes between the three groups.

There is a paucity of information regarding the cost-effectiveness of SSRIs and TCAs in a UK setting. This review failed to highlight any study specifically focusing on lofepramine. Of the small number of UK studies that compare the cost-effectiveness of SSRIs with TCAs, all use decision-analytic methods and are based on assumptions regarding costs and outcomes, particularly regarding resource-use data, rather than directly observed data. Of the studies that have collected resource-use and outcome information directly, none produced estimates of cost-effectiveness in a ratio form. As they were based in different healthcare systems in the USA⁷⁹ and Czech Republic,⁸⁰ there is no reason to suggest that these results are generalisable to a UK setting. As their patents expire, the SSRIs will become cheaper, although not nearly as cheap as the old TCAs, and therefore this will not end the debate over cost-effectiveness.

Patient preference designs

Studies conducted to evaluate cost-effectiveness in naturalistic settings may need to be designed differently to those with a primary aim of comparing efficacy. Traditionally designed studies neglect the impact of patient preference.

In open-label controlled studies, participants may become less motivated to follow the treatment protocol if they are not allocated to their preferred treatment, and consequently not gain the full benefit of the therapy, a process that has been described as "resentful demoralisation".⁸³ In addition, participants with strong treatment preferences may refuse randomisation and therefore be excluded from trials. The numbers excluded may differ between study arms, and may appear either to increase or to decrease the effect of individual therapies.⁸⁴ Other potential biases related to preference include an effect on potential participants' willingness to join a study,⁸⁵ restricting generalisation of the results. These concerns have led some investigators to suggest alternative study designs that allow for participant preferences, or

attempt to measure their potential effects. These different methods and their advantages and disadvantages are discussed here.^{86–89}

Zelen suggested a design in which patients are randomised to treatment arms before giving consent to the study, and efforts are made to ensure that the numbers changing arms are minimised.⁸⁹ Consent is not sought from those receiving usual care. These participants are assumed to be at no disadvantage by taking part, and outcome measures are limited to information usually recorded in medical records. The advantage of this design is that patients in the control group are not disappointed as they are not aware that they could have received the experimental treatment, removing this possible source of bias. However, this design is rarely used as a result of concerns about consent, and differential dropout rates occurring between the two groups as a result of different levels of information being given to participants in the two groups.

A partially randomised design has been suggested by Brewin and Bradley, and represents the preferred design in the majority of studies conducted on issues relating to preference.⁹⁰ Patients who express strong treatment preferences are allowed their desired treatment, while those who do not have strong views are randomised conventionally between the treatments available in the study. Both groups are followed up using the study outcome measures. However, the preference arms cannot be compared directly with the randomised arms, as baseline differences associated with preference may confound the effects of preference on outcome.⁹¹ Therefore, at least one analysis needs to be a comparison between the two randomised arms alone, and analyses that include the non-randomised groups have to be treated as observational studies with known confounding factors adjusted for in the analysis. Improvements have been suggested by Torgerson and colleagues, who recommended describing these confounders more precisely by eliciting the strength and direction of patient preferences before randomisation,⁸⁶ and by Olschewski and Scheurlen, who suggested that an analysis using randomisation status as a covariate might be helpful.⁹²

Rucker proposed an alternative approach, in which randomisation was separated into two stages.⁸⁷ In the first stage all patients are randomly allocated to one of two groups, the random group and the option group. At the second stage, patients in the random group are randomised a second time to the two treatment

options, whereas patients in the option group are given a free choice between the two treatments. Differences in treatment response between the random group and the option group may be due to self-selection by choosing treatment or the effects of suggestion as a result of receipt of the preferred treatment. Rucker developed a linear model to estimate these effects separately and was able to apply this to test statistics, which were approximately normally distributed.⁸⁷ However, this trial design cannot account for those who refuse the first stage randomisation, and the entire group is still not randomised between the two treatment arms. A similar trial design was proposed by Wennberg and colleagues.⁸⁸

Rationale for design of current study

As reviewed above, depressive illness is a major public health problem, and imposes a substantial economic burden, a large part of which results from the costs of recognising and treating depressed patients in primary care. A review of the existing literature reveals few data to inform evidence-based cost-effective prescribing. There is thus a clear need for a prospective, pragmatic RCT of the costs and benefits of antidepressant prescribing in UK primary care settings.

The classes of antidepressant drugs evaluated in this study (TCAs and SSRIs) are appropriate, as there is a lack of general agreement on which class is the most appropriate first line treatment in primary care. Lofepamine was included as a third treatment option, as many consider it to be a better tolerated and safer alternative to traditional TCAs such as amitriptyline and dothiepin. Although there have been many previous randomised controlled trials of TCAs and SSRIs, none has used a fully representative sample of depressed patients in primary care (e.g. because they have limited the sample to those patients with 'major depressive episodes'), whereas this study allows for the inclusion of patients with depressive symptoms of such a degree as usually lead to antidepressant prescribing in primary care. This study incorporated a preference design to allow patients and doctors with strong treatment preferences to be involved in the study, and not become lost to 'resentful demoralisation' should they not be allocated to their preferred treatment. The study design also includes measures to assess 1-year clinical outcomes, and the costs of primary and secondary care health services, in contrast to the majority of studies, which are of shorter duration.

Chapter 2

Methods

Introduction

Aim

The principal aim of the study was to compare the cost-effectiveness and cost-utility of the initial choice of antidepressants in general practice between TCAs, SSRIs and lofepramine (LOF). It should be stressed that it was the effect of the initial decision that was being tested, as patients may have switched treatments subsequently.

Design

The study was designed as a pragmatic, randomised, open-label trial of treatment with three classes of antidepressant. The objective was to recruit a representative sample of patients identified by their GPs as suffering from a new episode of depression.

Sample size

The study was designed based on the assumption that the three arms would have equal clinical effectiveness. Based on the report of Simon and colleagues,⁷⁹ and assuming that the effect size was similar, the sample size was calculated as follows:

Mean log cost = 7.16 (95% CI 7.00 to 7.32)
 Standard error = 0.08 (0.32/4) ($n = 155$)
 Therefore, standard deviation = $0.08 \times \sqrt{155} =$
 approximately 1.0

To demonstrate equivalence of cost to within 5% of the mean, that is, effect size 0.36 ($= 0.05 \times 7.16$) at 90% power, and allowing for three groups ($\alpha = 0.05/3$), the study required approximately 260 patients per group. There was an average 10% dropout after randomisation in the study by Simon and colleagues,⁷⁹ suggesting that randomisation should continue until 300 patients had entered each of the three arms. If the dropouts all entered the non-randomised comparison group (preference arm) that would comprise 135 patients. If 20% refused consent to the study procedures, it was calculated that entry would need to be offered to 1200 patients, to give an ITT analysis of 300 per group.

Setting and ethics committee approval

Initially, 102 general practices in the Wessex region were approached, with whom the authors

had previously collaborated on depression research. From past experience, it was expected that each GP would be able to start one patient per week on a new course of antidepressants. Thus, it was estimated that up to 60 patients per GP could be eligible for recruitment during the study period, suggesting a need to recruit a minimum of 20 GPs, although the authors were aware that these assumptions might be optimistic and that they would probably need to recruit more.

Ethical approval was applied for in the first instance from the three Hampshire local research ethics committees (LRECs), namely Southampton and South West Hampshire, Portsmouth and South East Hampshire, and North and Mid-Hampshire.

It became apparent that the number of practices that could be recruited in these areas would be insufficient to provide the number of referrals needed, so ethical approval was extended to other surrounding areas. As the intention was to recruit from more than three areas in all, approval was then applied for from the South and West multicentre research ethics committee (MREC). Following approval from the MREC, approval was successfully applied for from the LRECs covering East Dorset, West Sussex, North Wiltshire, South Wiltshire and South West Surrey.

Owing to the complexity of the study and various practical problems that were encountered, several protocol variations were made. The section below ('Patient recruitment, consent and randomisation procedures', p. 14) describes the final study design, after which modifications to the original protocol are detailed.

Practice and GP recruitment procedures

Contacting and recruiting practices

Once ethical approval had been achieved, all the practices within the relevant LREC's area were contacted. Initially this was done by letter (see Appendix 1), and this was followed up with a telephone call to the practice manager around 2 weeks later, to give the GPs a chance to discuss it. If interest was expressed by any of the GPs in

the practice, one or two members of the Assessing Health Economics of Antidepressants (AHEAD) study team or steering group visited the practice to explain in more detail what the study involved and answer any questions the GPs had about it. Wherever possible, one of the AHEAD team visiting the practice was also a GP (usually AT or TK), as it was felt that a GP would better understand any practical concerns the practice had about how the study might run in their practice, or any clinical issues about how involvement might affect their usual consulting, prescribing and referral patterns.

Service support costs

The GPs were offered no financial incentive to participate in the study, but were reimbursed £13 per patient recruited. This money for service support was provided through an ad hoc funding arrangement from NHS research and development (R&D). This amount per patient was calculated on the basis of 15 minutes of GP time at £40 per hour for the extra work involved in patient recruitment, and 20 minutes of reception/filing clerk time at £9 per hour, for the extra work in retrieving and filing patient records.

Newsletters

During the course of the study four newsletters were written and sent out to all participating GPs, to keep them informed of progress and to encourage them to remember to refer suitable patients.

Patient recruitment, consent and randomisation procedures (assignment and masking)

Inclusion and exclusion criteria

All adult patients diagnosed as having depression by the GP according to their usual practice and accepting antidepressant treatment were eligible to be randomised, including those with co-morbid physical or mental illness and patients over 65 years of age. It was recognised that the study would also include patients without a formal International Classification of Diseases (ICD-10) depressive episode (although the planned standardised assessments could distinguish those in the ICD-10 category at treatment initiation). Restricting entry to ICD-10 depressive episode would not reflect the reality of prescribing in primary care. Katon and colleagues⁹³ and others have criticised the use of psychiatric diagnostic criteria as inclusion requirements in primary care studies.

Patients were excluded if they were under 18 years of age, pregnant or breast-feeding, had a terminal illness, a confusional state or poor English skills, or were a temporary resident. Patients who were already taking antidepressants for depression or were commencing treatment for a non-depressive indication such as analgesia, insomnia, anxiety disorders, bulimia nervosa or obsessive-compulsive disorder were also excluded.

GPs were given a laminated, coloured, A4 sheet to be kept in a prominent place in the consulting room (see Appendix 2), containing details of inclusion and exclusion criteria.

Initial recruitment by the GP

The patient recruitment process is illustrated in *Figure 1*. In the finally adopted design, participating GPs were asked simply to gain initial consent from an eligible patient, at the time of initial diagnosis of depression in the surgery, to see a member of the research team to discuss their possible involvement in the study. A brief patient information sheet (1) was designed for the GP to give to the patient to read before seeing the researcher (see Appendix 3). An initial patient consent form (I) was signed by the patient indicating their agreement to be contacted by the researcher and discuss the study in more detail (see Appendix 4), the GP assuring the patient that they would be seen within a few days at most. The GP then sent a fax with the patient's contact details to the research team as soon as was convenient (usually on the day of the initial surgery contact).

Arrangements for initial antidepressant prescription

The GP had the choice of arranging a follow-up surgery appointment with the patient for prescription of the relevant drug treatment following randomisation by the researcher, or arranging to issue the prescription without seeing the patient for a second consultation. This decision, together with the date of the proposed consultation or prescription, was indicated on the initial consent and fax form (see Appendix 4).

GP drug preference information

An additional form was also faxed to the study team which included a statement by the GP as to whether they were happy for the patient to be prescribed a medication from any of the three antidepressant groups used in the study, and if they were not, the main reasons why not (Appendix 5). It also asked the GP to indicate whether the patient was suffering from any

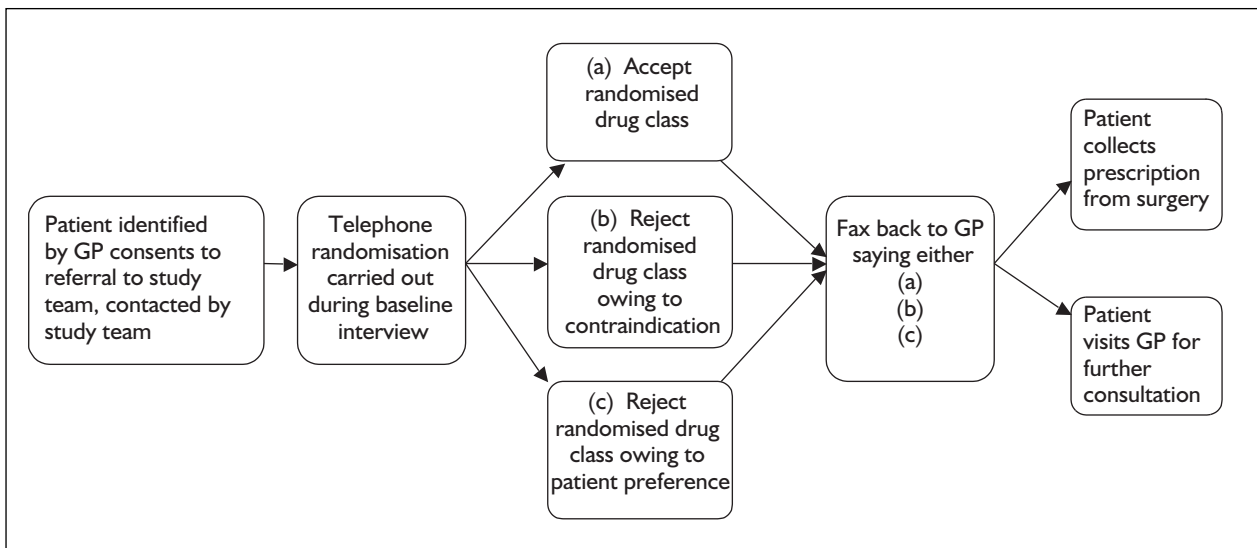


FIGURE 1 Flow diagram to show the partial preference design used

co-morbid disorder of which the research team needed to be made aware, whether the patient had been treated with an antidepressant before, and if so which of the three classes, or which antidepressants outside the three classes, had previously been used. A third form also asked which type of antidepressant the GP would have prescribed to initiate treatment, if the patient had not been participating in the AHEAD trial, either from the drugs allowed within the three AHEAD classes of drug, or another drug. They were also asked to give an indication of the strength of their preference for a particular drug, and the reasons for it (see Appendix 6).

Baseline visit

A member of the research team then contacted the patient, usually by telephone (but in a few instances by post) and arranged the baseline interview visit. This was usually arranged to take place in the patient's home, but could be at the doctor's surgery if the patient so wished, and if the surgery was able to provide a room. The time of the visit was arranged at the patient's convenience, and was frequently in the evening, after work hours, or less frequently at the weekend.

At the baseline visit the researcher then described the project in detail, asked for and answered any questions the patient had, and obtained informed consent using patient consent form II (see Appendix 7). The researcher then proceeded to carry out the baseline interview (see 'Measures' section, p. 18, for details of the measures that were administered), and then telephoned the randomisation service to determine the arm of the study to which the patient should be allocated.

Patient drug preference and reasons

Once the allocation had been obtained, the patient was given an information sheet on the allocated medication class (see Appendix 8). The patient then signed consent form III, either agreeing or not agreeing to take the allocated medication. If the patient declined to take the medication they were asked to give reasons for this on consent form III (see Appendix 9).

If the patient consented to participate in the study, there were two possible outcomes. First, the patient might consent to the allocated treatment, in which case a drug would be chosen from within the class allocated and the study would proceed. Second, treatment might proceed outside the allocated class, either because the patient did not consent to the class (for whatever reason) or because the GP believed that there was a medical contraindication. Refusals of the allocation were recorded. It was anticipated from previous research⁷⁹ that about 15% of those who consented to participate in the study would refuse the allocated treatment, but because they were to stay in the study they would still provide valuable information about relative treatment acceptability and costs. The reasons for non-acceptance of randomisation were recorded and the patients treated as clinically appropriate.

Choice of treatment agreed between doctor and patient

As soon as possible after the baseline visit, information was fed back to the GP by fax, giving the randomly allocated drug class. The fax form varied according to the GP's previous indication of preference for a particular drug or class of drugs,

and the patient's expressed willingness or unwillingness to take a drug from the allocated class (see Appendix 10 for the three different forms). The GP was then asked to decide what drug to prescribe, in the light of this information, and to feed back the treatment decision on the fax form previously sent to the GP informing them of the randomisation to the research team (see Appendix 10).

Guidelines were given to the GPs in an attempt to standardise their prescribing to an extent (see section 'Treatment schedules', p. 21, for details, and Appendix 2). The instructions included a recommended starting dose and escalation schedule, which varied according to the class of drug and age of the patient. The GPs were also told that the prescribed treatment could be changed as clinically indicated, and asked, if possible, to continue the full dose for 6 months after remission, or to continue until the end of the 1-year study period if the patient had previously suffered two or more attacks of depression within the past 5 years. These instructions were included on the laminated A4 sheet containing the inclusion and exclusion criteria, provided for display in a prominent position in the consulting room (see Appendix 2).

Partial preference design

The design of the current study reflected the desire to minimise the effect of treatment choice on recruitment, and to improve the ability of the study to assess the effect of receipt of preferred treatment on outcome. The two-stage consent process allowed participants to register for the study and agree to complete outcome measures without committing themselves to accept particular treatment options. During this process they were given general information about the study, but remained blind to the treatment allocation.

Having agreed to take part in the study, all participants were randomly allocated to one of the three treatment options. Following the randomisation process, they were given detailed information about the treatment to which they had been allocated, but not about the alternative treatment arms. The information given was based on the medication data sheet and was designed to reflect the situation in clinical practice, where patients receive a patient information sheet in the pack of tablets. After receipt of this information sheet, participants had an opportunity to express a preference by accepting or rejecting the offered treatment. In the event that they declined the allocated treatment, they returned to their GP and

together chose one of the alternative treatments on offer. At the initial referral, doctors indicated whether there was a medical contraindication to individual treatment arms. If the allocated treatment was contraindicated, then participants were referred directly back to their doctor to choose an alternative treatment without being given the opportunity to accept or decline the allocation.

This design overcame 'resentful demoralisation' by allowing patients to participate while still being able to receive their preferred treatment, and therefore potentially maximised the extent to which participants were representative of all patients being treated for depression in the community. In addition, unlike the partially randomised design, the effect of receipt of preferred treatment on outcome can be estimated by making a comparison between all participants analysed on an ITT basis, and on conclusions drawn from those who agree to accept the treatment to which they are randomised.

At the start of the study, it was realised that this design brought with it a number of potential difficulties as well as benefits. By involving the GP on more than one occasion in the recruitment process for some participants, there was a risk that some doctors would be reluctant to recruit into the study. The two-stage consent procedure introduced a delay between diagnosis and receipt of treatment, potentially putting seriously ill patients at risk if they participated in the study. These difficulties were overcome by minimising doctors' involvement in the recruitment process as far as possible, and providing the option for a home visit by a member of the study team within 24 hours. Doctors were asked to avoid recruiting seriously ill individuals who might require more urgent care.

Modifications made to originally intended protocol

Consent and randomisation procedures

The randomisation process was first modified before the start of the study, and the recruitment process was subsequently changed again during the early part of the study to enhance recruitment and address the difficulties that practitioners encountered in incorporating the project into clinical care.

Initially, a two-stage blocked randomisation stratified by GPs had been envisaged, the aim being to assign all eligible patients to one of the

three treatment groups before patient consent to participation had been secured. Although this was an unusual method, it offered initial randomisation of the whole of the index population, thus potentially improving the generalisability of the trial. To discourage selection bias, in the original design the allocation to treatment arm was to have been preprinted onto no carbon required (NCR) paper and contained within two opaque envelopes. The GP would then write the patient's name and number on the outside of the first envelope, which would transcribe automatically onto the NCR paper within the second inner envelope. An information and consent sheet about the study would be contained inside the first envelope, accessible only after the seal was broken. If consent was refused, the GP would return only this sheet, which would not contain the patient's name. If consent was given the second envelope seal would be broken to reveal the treatment allocation to the GP and the patient. This group had successfully used this method in a previous study, but the National Coordinating Centre for Health Technology Assessment (NCCHTA) was concerned that this might not be a secure method of randomisation, and might still permit conscious or unconscious allocation bias by the GPs. The NCCHTA therefore insisted, before the study started, that the method be changed to remote telephone randomisation accessed by the GP.

Four months into the study a decision was made to reconsider the consent and randomisation procedure. The rate of recruitment was much slower than anticipated, at around 11 patients per month instead of the 60 hoped for, and the dropout rate was around 25% between recruitment by the GP and the baseline interview by the researcher. The participating GPs, who were experienced in recruiting successfully for other studies, complained that the whole process of gaining consent and randomising the patient was simply not possible during routine booked surgery consultations. The diagnosis of depression and seeking of agreement to antidepressant treatment would typically take considerably longer than the average 10-minute GP appointment anyway, even before consideration was given to recruitment to the study. The length of time it took for the patient to read the information sheet and sign the consent form, followed by the GP telephoning the randomisation service, then writing out the prescription for the allocated treatment, was prohibitive in many cases and was affecting the recruitment rate significantly, in the opinion of these experienced GPs.

The procedure was therefore modified to that described above, in which in the first instance the GP would simply gain consent from the patient to see a researcher. The researcher was then able to describe the project in detail and take the patient through the whole consent and randomisation procedure. The patient would then return to the GP for a prescription of the allocated treatment at a second, prearranged consultation.

The advantages of the new procedure were that the GP's time would not be wasted, and the consent would be obtained in a relaxed atmosphere in the patient's home, by a researcher more familiar with the study and able to answer all the patient's questions. This, it was hoped, would mean that, once consent had been given, the patient would be more likely to remain in the study. It was also possible for the researcher to complete the baseline interview before telephoning the randomisation centre for allocation to treatment arm, removing the possibility of observer bias, as all the measures would then necessarily be completed blind to allocation.

One possible disadvantage was that the GP could not start treatment straight away at the consultation in which the depression was diagnosed, which might deter some of the GPs from asking some of the patients to take part. To reduce this possibility, the researchers informed the GPs that in exceptional cases they would carry out the consent procedure, baseline interview and randomisation within 1 day of referral of the patient to the study team, if not on the same day.

This modified procedure still allowed the patient and doctor to consider the proposed allocated treatment class and to decide on a different choice of treatment at the second consultation, in which case the patient would be included for analysis in the preference arm. This approach proved more acceptable and recruitment improved considerably. For the first 28 weeks, the study recruited patients using the original protocol. This resulted in 72 patients being referred, but only 49 actually agreeing to baseline interviews (68%). The new protocol, for the same period, resulted in 93 referrals, with 80 agreeing to baseline interviews (86%).

Frequency of follow-up and face-to-face contacts

It was originally intended that patients would complete postal questionnaires each month (see 'Measures' section, p. 18) for the duration of the

TABLE 2 Data collected at each time-point

Questionnaire	Baseline	1 month	2 months	3 months	6 months	9 months	12 months
CIS-R	✓			✓	✓	✓	✓
HADS	✓	✓	✓	✓	✓	✓	✓
SF-36	✓			✓	✓	✓	✓
EQ-5D	✓	✓	✓	✓	✓	✓	✓
UHSS	✓	✓	✓	✓	✓	✓	✓
Sociodemographic	✓						

study. These were to include the following information:

- Use of Health and Social Services (UHSS)
- Hospital Anxiety and Depression Scale (HADS)
- EuroQol 5 Dimensions (EQ-5D)
- recall of days in the previous month when unable to carry out normal activity, either work or leisure
- current drug treatment: all categories
- standardised accident report.

They were to have face-to-face contact at baseline and after 3 months only.

Five months into the study it became clear that patients were finding the monthly postal questionnaires, including the HADS, EQ-5D and UHSS questionnaires, too onerous, and some were withdrawing altogether from the study when faced with the realisation that they were expected to continue completing the measures monthly for the whole 12-month follow-up period. It was therefore decided to drop the postal questionnaires for months 4, 5, 7, 8, 10 and 11, to reduce the workload for the patients. This meant that HADS–Depression (HAD-D) scores for effectiveness and EQ-5D scores for utility would be available only at baseline, 1, 2, 3, 6, 9 and 12 months.

Fifteen months into the study it was decided to increase the number of face-to-face contacts between researchers and participants. The response rate at that time was 46%, 24% and 38% at 6, 9 and 12 months, respectively, which was lower than hoped for. It was expected that face-to-face contacts would improve the rate of return of questionnaires, and encourage continued participation beyond the 3-month interview. The final response rates improved to 62%, 57% and 52%, respectively.

Twenty months into the study a decision was taken to reduce the workload on patients still further, by

dropping the requirement for them to complete the diary on use of health services and antidepressant drug treatment. The form used to collect these data was not being completed on a regular basis by the majority of participants, some of whom just discarded it. It was decided that the use of health services and antidepressants prescribed was better assessed retrospectively with the patient at the 3-, 6-, 9-, and 12-month face-to-face assessments, and through the general practice records after the end of the 12-month follow-up.

Audit of prescribing outside the study

In the original proposal, it was planned at the end of the study to audit the prescription of antidepressants by participating GPs, through their computerised practice records, to estimate the proportion of patients referred to the study out of all those to whom they had prescribed a new course of antidepressants. However, the application of the 1998 Data Protection Act meant that it was no longer acceptable for an outside researcher to download and analyse the prescribing records of patients who had not specifically consented for their information to be accessed in this way. Participating practices could not allocate the time of their own staff for this process. Regrettably, therefore, the audit was dropped.

Measures

Summary of measures used

For each patient there were three types of data to be collected: interview data at baseline and after 3 months, self-rating scales at 1, 2, 3, 6, 9 and 12 months, and a review of healthcare records after 12 months (*Table 2*).

Face-to-face contact took place with the patient at baseline (as soon as possible after recruitment) and at 3 months' follow-up. Clinical features were

assessed using the CIS-R,⁹⁴ which can be used to generate a diagnosis according to the ICD-10. The computerised version (PROQSY) was used. The Short Form 36-item generic health status measure of the Medical Outcomes Study (SF-36) was also administered at the baseline interview.

Self-rated assessments were completed at 1, 2, 3, 6, 9 and 12 months, referring to the preceding week. Patients were asked to return these within 1 week of each census date, and if they were more than 2 weeks late they were discounted.

They included:

- use of health services in the previous month according to a standard schedule, including contacts with the GP in surgery and at home, contacts with other practice staff, contacts with community mental health teams, and psychiatric and general hospital contact, including accident and emergency (A & E) departments
- the HADS
- the EQ-5D, an instrument for describing and valuing health-related quality of life, including a health state classification system and a thermometer-style visual analogue scale
- recall of days in the previous month when participants were unable to carry out normal activity, either work or leisure
- current drug treatment: all categories
- a standardised accident report.

Healthcare records were reviewed at 1 year. Primary data on resource use were obtained from the patient interviews and self-ratings. Information was also collected after the end of the 12-month follow-up period from the practices' computers, manual records and secondary care sources where appropriate. Although it was likely that no single source of information would be fully reliable, each was likely to lack sensitivity rather than specificity, such that the presence of an event was more likely to be true than the absence of an event. The collection of data from several sources allowed cross-validation of events, and the study was inclusive rather than exclusive where there appeared to be a discrepancy between sources.

Detailed description of measures

CIS-R

The CIS-R⁹⁴ was used to generate total symptom scores and diagnoses according to ICD-10.⁹⁵ Diagnoses were generated using the algorithm used in the OPCS national surveys of psychiatric morbidity in Great Britain.^{11,96} The CIS-R was completed by the patient on a laptop computer

(PROQSY version), which minimises the possibility of interviewer rating bias and the need to consider inter-rater reliability issues.⁹⁷

HADS

The primary clinical outcome measure was weeks free from depression, measured using the HADS.⁹⁸ This is a self-report questionnaire consisting of 14 items. Weeks free from depression were defined using the depression (D) scale of the HADS, where a score of less than 8 indicates no depression.

EQ-5D

The EQ-5D is a generic instrument for measuring health-related quality of life.^{99,100} Respondents were asked to categorise their current health state in terms of five domains of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), where each domain has three levels. Each patient's health state was then assigned a value or 'utility' on a scale of 0 (dead) to 1 (full health). These values reflected the relative preferences for health states, and were used to form QALYs.

A predefined set of values or 'tariff', based on a large representative sample of the UK population, was applied to each patient's EQ-5D health state.^{101,102} Thus, each patient in the trial describes his or her own health, and the utility score corresponding to that description of health is derived from a population sample.

SF-36

The SF-36 is a questionnaire consisting of 36 items concerning respondents' health-related quality of life.¹⁰³ The responses to the items can be condensed into scores on eight domains of health-related quality of life: physical functioning, role-physical, role-emotional, social functioning, pain, vitality, mental health and general health. Scores on each of the domains are normalised to range from 0 to 100.

Data quality control

Ten per cent of the forms that had been processed using either scanning or punching were re-entered a second time to check for reliability and accuracy. This was done towards the end of the study and incorporated the entire patient database. The patient paper files were selected for their completeness of data returned; this seemed to be the most practical and time-efficient way of selecting the required number. The completed questionnaires were then entered on a form in Microsoft Access. These were then reconciled with the previously entered data.

TABLE 3 List of resource-use items collected from GP records

Resource	Information collected
Attendance at day hospital	Date of visit
Attendance at midwife clinic	Date of visit
Attendance at psychiatric clinic	Date of visit
Clinic visit with member of community mental health team	Date of visit
Contact with GP	Date of contact; whether contact was by telephone, at surgery or at home
Contact with healthcare assistant at clinic	Date of visit
Contact with physiotherapist	Date of contact; whether contact was at hospital, at surgery or elsewhere
Contact with practice nurse at surgery	Date of visit
Day patient for surgery	Date of visit
Home visit by chiropractor	Date of visit
Home visit by community psychiatric nurse	Date of visit
Home visit by district nurse	Date of visit
Home visit by emergency ambulance service	Date of visit
Home visit by health visitor	Date of visit
Hospital clinic attendance (non-psychiatric)	Date of visit
Hospital inpatient admission	Admission and discharge dates; whether admission was psychiatric or non-psychiatric related
Radiology services (e.g. ultrasound, mammogram)	Date of procedure
Visit to A&E department	Date of visit
Visit to chiropractor	Date of visit
Visit to community psychiatric nurse at clinic	Date of visit
Visit to counsellor at surgery	Date of visit
Visit to occupational health service clinic	Date of visit

Review of healthcare records

Procedure for data collection

The managers of the participating practices were contacted and a mutual time was agreed for the researchers to visit the surgery premises. A letter of confirmation was sent to each manager, along with a list of patients whose medical record data were to be collected. The researchers took along copies of the consent forms signed by the patients at the time of randomisation; although the practices were expected already to have copies of these, it proved useful sometimes to take further copies to avoid any doubt about patients' consent to have their records examined.

The practice managers or other members of their staff helped the researchers to access the computerised records of participating patients and become familiar with any computer codes used by the practice. Information on health service use and medication prescribed was usually extracted from the 'Journal or Consultation' and 'Medication or Therapy' fields. The handwritten

case notes were also examined, to add to, confirm and clarify the computerised records.

Resource use data collected

General practice and hospital use

NHS resource-use data were collected for all patients using GP records. *Table 3* and Appendix 11 outline the health service use items that were extracted from the practice records.

The following assumptions were made.

- Blood tests and phlebotomy were removed unless another specific contact was referred to, such as 'practice nurse'.
- 'GP admin' was removed owing to ambiguity of data collected.
- 'District nurse' was removed.
- If no dates or details were available for counselling sessions, 6 sessions over six weeks was assumed.

Medication

All medications, including those unrelated to the

treatment for depression, prescribed for the patient during the 12-month period following randomisation were recorded from the computerised and written practice records. The recorded items related to prescriptions were: prescription date, medication name, formulation, dose per day units, number taken at each dose, times taken per day, and total size of prescription (quantity and units). This information represented the prescriptions issued, and it was recognised that it did not imply that the prescriptions were cashed or the medication was taken by the participating patients.

The following assumptions were made.

- If no total amount was listed in the 'total tab' field for an antidepressant, then a 1-month prescription was assumed.
- If no total amount for any other medication was listed in the 'total tab' field, then the British National Formulary (BNF) was referred to and the original pack size was used.
- If no total amount was listed in the 'total tab' field but was mentioned elsewhere in that patient's record, then that amount was assumed.

Data entry

Three different methods were tried for collecting and entering the data from the GP surgeries. Initially, individual computerised forms for each entry were designed, using SPSS. These proved to be very time consuming, but provided useful information on which to write a database. Paper forms were then used in an attempt to reduce the time taken to enter the data, but this only resulted in duplication of the task. The final system, which proved to be most efficient and reliable, was a Microsoft Access data entry system, designed to record the health service use and medications prescribed from the GP surgery records, which was entered directly on the researchers' laptop computers at the practices. These records were then added to the master database on return to the university.

Data integrity

A review of 10% of computer and paper records collected by three different researchers revealed some anomalies. As the data were collected at different points in time, anomalies could have resulted from both inter-rater and test-retest sources. Likely reasons for discrepancies included the following.

- The formatting of the data was inconsistent.

- There was some information missing in individual fields.
- There were duplicate entries.
- The records changed over time.
- The timespan of the data collected may have varied.

It was not feasible to double-enter the data set within the resources available, and therefore the solution agreed was for the researcher to go through the data and clean them, paying specific attention to the relevant items highlighted above. The patient-completed healthcare data were also incorporated and used for assigning costs, as the main threat to validity was missing costs, not overestimation.

Treatment schedules

The researchers wished to identify any differences in outcomes as a class effect, comparing TCAs with SSRIs with lofepramine, rather than trying to measure differences between single drugs representing each class. It was believed that offering a choice within each class would enhance recruitment of practitioners and patients to the study. The three arms therefore consisted of the following classes of antidepressant.

- TCAs: a choice of amitriptyline, dothiepin or imipramine was offered. At the start of the study, the first two were the most commonly prescribed TCAs, according to general practice prescribing data, accounting for 16% and 13%, respectively, of all antidepressant prescription days in 1996/97. Imipramine, while not frequently prescribed in the UK, was the most commonly prescribed in the USA and offered a less sedative alternative within the same class.
- SSRIs: the three most prescribed drugs according to prescription data were fluoxetine (18% of prescription days), paroxetine (13%) and sertraline (13%). All were therefore available as treatment choices in the study.
- Lofepramine: this was included as a relatively commonly prescribed second generation antidepressant. Other drugs in this category (which is not a class as such) such as trazodone or maprotiline, were very seldom used at the time when the study began, and were therefore not included.

Between them these treatment choices accounted for approximately 75% of all general practice antidepressant prescriptions nationally.

TABLE 4 Recommended dosing schedule

Type of antidepressant	Age (years)	Dose
TCA	18–65 >65	50 mg rising in 25-mg weekly steps to a maximum of 150 mg 25 mg rising in 25-mg weekly steps to a maximum of 125 mg
SSRIs	Fluoxetine Paroxetine	20-mg daily dose throughout 20-mg increasing to 30 mg after 3 weeks and to a maximum of 40 mg after 6 weeks
	Sertraline	50 mg increasing to 100 mg after 3 weeks and to a maximum of 150 mg after 6 weeks
	Lofepramine	70 mg rising in weekly 70-mg increments in divided doses to a maximum of 210 mg

Dosage schedule

To prevent the antidepressants being given in too low a dose, the participating GPs were given standardised prescribing instructions including starting doses and recommended escalation schedules to be followed unless recovery from depression or intolerable side-effects supervened, based on existing guidelines¹⁰⁴ (see Appendix 2). The recommendations are shown in *Table 4*.

The TCAs needed to be titrated from a subtherapeutic starting dose to avoid side-effects during early treatment. The highest recommended doses of the TCAs were considerably higher than those used routinely in general practice. The slower recommended escalation of SSRIs reflected a difference in their purpose. The starting doses of all three SSRIs have been found to be superior to placebo in randomised trials, but escalation would allow for individual dosing according to patient need. Thus, for all treatments, individual patients would receive a dose in the therapeutic range, unless they were unable to tolerate this dose or recovered on a lower dose (whether or not recovery was due to the antidepressant).

If the patient recovered, then continuation antidepressant treatment was recommended at full dose for a further 6 months. Thereafter, continuation to the end of the 1-year study period was recommended if the patient had previously suffered two attacks of depression within the preceding 5 years.

In the event of first line treatment failure after 6 weeks, other clinically indicated treatments were allowed, to be monitored as part of the study. Referral to secondary care was allowed at any point, and any other medication or treatments available in the practice setting could be used as

appropriate at any time. Each of these eventualities was part of the outcome of the study, and was therefore not predetermined in the treatment protocol.

Statistical analysis

Approach to analysis

The trial was designed as an equivalence trial for costs. The power calculation is shown in the Introduction to this chapter. It has been argued that ITT analysis may not be appropriate for equivalence trials because it biases the study towards accepting the null hypothesis.¹⁰⁵ The opposite approach is per-protocol analysis, whereby the data on each patient are split according to the time spent on each drug, and summed for each drug. However, it was decided that the main analysis of the clinical efficacy variables should be by ITT, since this answers an important clinical question. It was also decided to analyse the economic data using ITT, as a timelag between drug effect and resource use incurred would otherwise make comparisons difficult. The analysis first included all patients regardless of whether or not they accepted their randomisation. The analysis was then repeated including only patients who accepted their randomisation. The results from the two analyses were then inspected for differences.

The data were checked to see whether outcomes for patients for whom the randomised drug was rejected because of the patient's or doctor's preference were different to outcomes for the randomised arms.

The primary clinical outcome, the number of weeks free from depression (HAD-D <8), was analysed by repeated-measures analysis of variance (ANOVA).

The repeated-measures ANOVA model for depression-free weeks (DFWs) was:

$$y_{ijk} = \mu + p_{ij} + t_k + (ht)_k + (gt)_{ik} + e_{ijk}$$

where $i = 1, 2, 3$ (allocation groups: LOE, SSRI, TCA), $j = 1, 2, 3, \dots, n_i$ (patients, where $n_i =$ number of patients in group i), $k = 1, 2, 3, 6, 9, 12$ (months), y_{ijk} is the HAD-D score (continuous) for the j th patient in group i at time k , μ is the overall mean DFW, p_{ij} is the random effect associated with the j th patient in group i , t_k is the effect of time k , $(ht)_k$ is the effect of the baseline HAD-D score at time k , $(gt)_{ik}$ is the effect of group i at time k , and e_{ijk} is the random error associated with the j th patient in group i at time k .

No assumption was made about the correlation between responses at different time-points on the same patient. Missing data were assumed to be missing at random (MAR). The model was fitted using the MIXED procedure in SAS version 8.2 (SAS Institute, Cary, NC, USA). Estimates of group means and their differences (at month 12) are reported, together with their associated 95% confidence intervals.

The TCAs were used as a base comparison against which to judge the cost-effectiveness of the other two newer classes. All three classes of drugs were compared against each other for their effectiveness and cost-effectiveness.

Time was calculated from the date of randomisation for each patient to either 12 months from randomisation or the date of censoring. Patients who were lost to clinical follow-up were censored at the time of their last known contact.

Missing data

HADS: depression-free weeks

At each time-point, patients were categorised as being depressed (HAD-D <8) or not depressed (HAD-D >8). To estimate the number of depression-free weeks a linear interpolation method was used. If successive HAD-D scores fell either side of a score of 8, a line was drawn joining the two, and the time-point at which the line cut the value of 8 was taken as the time when an episode started or finished.

Values missing with observed values to either side (internal) were assumed to be greater than or equal to 8 if both observed values were greater than or equal to 8, and less than 8 if both observed values were less than 8. If one observed value was less than 8 and the other greater than or

equal to 8, the interpolation was carried out on the observed value.

Values of HADS missing before the end of follow-up and with no subsequent values (external) were treated in one of two ways. The first method assumed that the estimate was truncated at the last observed value, and this estimate was weighted by the number of weeks the subject had been in the study. For the truncated values, the assumption was made that the subsequent missing values were MAR. MAR assumes that the probability of an observation being missing depends on the observed data but not on the actual missing observed value, once the covariates are accounted for. Fairclough¹⁰⁶ (p. 77) explains that this is not uncommon in longitudinal studies. Thus, someone may recover and so not be willing to turn up for assessment. However, because the HADS values before the missing value had been observed and this event could be predicted, this implies that the missing values are ignorable (Fairclough, Appendix 3).¹⁰⁶ It has been shown that valid estimates of treatment effects can be obtained in this case. The number of depression-free weeks is again estimated by linear interpolation. The advantage of this method is that it estimates the number of depression-free weeks for the whole follow-up period, and so no weighting is required. This means that the clinical effect can be directly related to the costs, which are not weighted.

In the analysis, it was found there was very little difference between treatment effects and confidence intervals estimated by either the truncation or the MAR method (i.e. month 12 estimates using repeated measures or weighting by length of follow-up). The MAR method was therefore preferred.

Intention-to-treat analysis

The original protocol specified that the data would be analysed in terms of four groups; each of the three treatment arms plus the preference arm. After further consideration, the trial steering group felt that a standard ITT analysis would be a more appropriate approach to the analysis of clinical outcome. The reason for this is that this is what would happen in practice if the clinician started by prescribing a drug in one of the three classes. Therefore, those patients who did not receive their allocated drug because of an expressed preference would be included in the treatment arm to which they were randomised. A sensitivity analysis would assess the effect of the preferences on the results by removing these patients from the data and repeating the analysis.

Economic analysis

Costs

The study took an NHS perspective throughout. All direct healthcare resource use was recorded and costed. Although the number of days on which patients were unable to carry out their usual activities was recorded, as well as data on accidents, given the NHS perspective, these were considered to be secondary outcomes in the study and were not costed.

For the cost data both the ITT and per-protocol analyses were assessed. The data were analysed on an ITT basis (such that patients were grouped according to the drug class of their initial randomisation). The analysis included all patients regardless of whether they accepted their randomisation, although a sensitivity analysis was conducted to include only those patients who accepted their randomisation. The results from both analyses were compared. Patients who were lost to outcome follow-up were censored at the time of their last known contact. Time was calculated from the date of randomisation for each patient to 12 months or to the date of censoring.

Description of costing procedure

Unit costs were obtained from published sources for the year 2001/02, and costs were inflated or deflated as appropriate where figures were not available for that year.¹⁰⁷⁻¹¹¹ All items of resource use relating to private treatment were assigned NHS unit costs. Records were obtained for GP appointments that were not kept by patients, but these were not assigned costs as they are included in the unit-cost estimates for GP visits.

All prescriptions were included in the total cost estimates for each patient in the main analysis. However, it was possible that particularly expensive drug treatments, unrelated to depression, for patients in one or more groups of analysis might skew the results of the analysis. Therefore, an additional analysis was undertaken including only those prescriptions considered to be potentially related to treatment for depression.

Cost-effectiveness analysis

Incremental cost per depression-free week

The effects of treatment were measured in terms of depression-free weeks, using the HADS to define 'depression-free'. Patients were categorised on a binary scale of depressed (HADS <8) and not depressed (HADS ≥ 8). Time spent in depression

(according to the cut-off value) was summed over the period. Missing values were interpolated using the method described above (section 'Statistical analysis', p. 22), which assumed a linear relationship between the scores immediately before and after the missing scores. The data were not extrapolated beyond the last observation.

An incremental approach was taken to the analysis of cost-effectiveness. Differences in costs and effects between the treatments were expressed using an incremental cost per depression-free week. Resource-use data were censored at the time of each patient's last known HADS score.

The ICER is defined as the ratio of incremental costs to incremental benefits from the treatment under consideration and is expressed more formally as:

$$\text{ICER} = (C_A - C_B) / (E_A - E_B)$$

where C_A is the mean cost of treatment A, C_B is the mean cost of treatment B, E_A is the mean effect of treatment A (in terms of depression free-weeks), and E_B is the mean effect of treatment B (in terms of depression-free weeks).

Thus, the ICER gives an indication of the additional cost required to provide an extra depression free-week. As the period of study was only 1 year, neither costs nor outcomes were subject to discounting.

Traditional methods for calculating confidence intervals rely on data being normally distributed. Cost data are typically skewed. Bootstrap methods do not require assumptions to be made about the distribution of data, and bias-adjusted non-parametric bootstrapping was used to calculate 95% confidence intervals around mean values in the analysis. Within the bootstrapping method, repeated samples of the data are taken, with replacement, to produce a distribution of mean values. Bootstrapping also has the advantage that it provides a method for calculating confidence intervals around ratios. However, within cost-effectiveness analysis, this relies on a reasonably large effect size of treatment. If the effect size is small, variations in the small denominator may lead to large fluctuations in the magnitude of the ratio.¹¹² Bootstrapped ICERs are presented on cost-effectiveness planes to illustrate the uncertainty around the overall mean ICER. The x axis of the plane indicates the incremental effectiveness (additional depression-free weeks) and the y axis indicates incremental costs.

Utility and health-related quality of life

Quality of life was measured using the EQ-5D classification system. Utility values from a large UK general population study were applied to enable the calculation of QALYs and cost-utility ratios. In addition, the self-rating SF-36 measure of generic health status was included every 3 months. This is not utility based, but is a well-established health-related quality of life measure. The five items in the SF-36 which comprise the MHI-5 mental health inventory have been shown to have good validity in measuring mental health status.

Incremental cost per QALY

A secondary economic analysis was performed on the data using QALYs as the outcome. A QALY is a measure that combines survival with a measure reflecting the 'quality' of that life. The survival component of a QALY is expressed using 'life-years gained' from treatment. The quality component comes from quantifying and valuing patients' health-related quality of life. This study used the EQ-5D classification system and a set of values from the UK population to measure the quality of life component of the QALY. Missing EQ-5D data were treated in the same way as for the HADS, such that missing data were interpolated assuming a linear relationship but not extrapolated beyond the last observation. In the absence of a survival difference between the two arms, the QALY reflects solely the differential in quality of life between the two groups.

Differences in the baseline utility values between groups may lead to biases in the results even if these differences are not statistically significant.¹¹³

Therefore, utility values were adjusted where differences at baseline were found. Utilities were adjusted using a univariate generalised linear model, including group as a fixed factor and baseline EQ-5D score as a covariate. Models were estimated separately for each of the time-points at which utility data were collected (1, 2, 3, 6, 9 and 12 months). Interpolation of missing scores was performed after adjusting for baseline differences.

As with the cost-effectiveness analysis, bootstrapped mean incremental cost per QALY ratios are presented on a cost-utility plane, where additional QALYs are represented along the x axis and incremental costs along the y axis. Results were subject to a threshold analysis using cost-effectiveness acceptability curves (CEACs). The amount that a health system can afford, or is willing, to pay for an additional QALY is known as the maximum acceptable incremental cost-effectiveness ratio (MAICER), and the cost-effectiveness acceptability curves reflect the probability that treatment is cost-effective for different threshold values or MAICERs.

Testing equivalence of costs

The costs associated with resource-use data were analysed for all patients to 12 months from date of randomisation, and a test was done for equivalence in cost between the three drug classes. The maximum acceptable difference (D) in costs was defined as 5% of the log mean cost of the TCA arm, as determined by the sample size calculation. Thus, for this sample, to demonstrate equivalence the 95% confidence interval for the difference in costs should exclude the range $-D$ to $+D$.

Chapter 3

Characteristics of the participants

GP recruitment

Recruitment took place between October 1999 and April 2002, and patients were referred to the study by 87 GPs from 55 practices (*Table 5*).

Patient disposition

Of the total of 388 patients (261 women, 127 men) referred, 25 patients declined further participation, when randomisation followed the first version of the study protocol. An additional 36 patients declined further participation, following the institution of the revised protocol for randomisation. Thus, 327 patients (84.3% of those referred) were available for randomisation and the baseline assessment.

As expected, there was attrition in patient numbers over the course of the study. A summary of patient disposition is shown in *Figure 2*. Three of the patients who underwent baseline assessment did not wish to participate further in the study, leaving a total of 324 (99.1% of those randomised) patients available for assessment at month 1. Nine patients declined further participation after that assessment, leaving 315 (96.3%) patients available for assessment at month 2. After this assessment, one patient was removed from the study following a non-protocol-related adverse event, and an

additional five patients declined further participation. A total of 309 (94.5%) patients were available for assessment at month 3. Twenty-four patients declined further participation in the study, and an additional 22 patients could not be contacted, leaving 263 (80.4%) patients available for assessment at month 6. Following this assessment, five declined further participation and 11 could not be contacted, leaving 247 (75.5%) patients available for assessment at month 9. After this assessment, two patients died, nine declined further participation and one could not be contacted, leaving 235 (71.9%) patients available for assessment at the end of the study.

Not all patients provided outcome data at each assessment. The month 3 assessment was performed throughout the duration of the study, but the patient assessments at months 6, 9 and 12 were introduced 13 months into the study period.

Demographic characteristics of referred and randomised patients

The 388 patients referred to the study team comprised 261 (67.3%) women and 127 (32.7%) men. The mean age was 42.6 years (age range 17–91 years). In total, 327 patients were randomised (*Table 6*). The proportion of men and women in the referred population and

TABLE 5 Summary of practices and GPs involved in the study

Ethics committee area	Practices that made referrals	Practices that made no referrals	Total practices	GPs who made referrals	GPs who made no referrals	Total GPs
East Dorset	12	3	15	20	22	42
North and Mid-Hampshire	12	9	21	17	41	58
North Wiltshire	5	0	5	5	3	8
Portsmouth and South East Hampshire	4	1	5	4	1	5
South Wiltshire	8	0	8	17	15	32
Southampton and South West Hampshire	13	4	17	23	18	41
West Sussex	1	1	2	1	9	10
Total	55	18	73	87	109	196

TABLE 6 Gender and age of patients randomised into the study

	TCA	SSRI	LOF	Total
Gender				
Male	37 (34%)	38 (35%)	33 (31%)	108 (33%)
Female	76 (35%)	71 (32%)	72 (33%)	219 (67%)
Total	113	109	105	327
Age range (years)				
17–29	25 (37%)	22 (32%)	21 (31%)	68 (21%)
30–39	27 (30%)	28 (31%)	36 (39%)	91 (28%)
40–49	21 (37%)	17 (30%)	19 (33%)	57 (17%)
50–59	21 (31%)	25 (36%)	23 (33%)	69 (21%)
60–69	11 (61%)	6 (33%)	1 (5%)	18 (6%)
≥ 70	8 (33%)	11 (46%)	5 (21%)	24 (7%)
Total	113	109	105	327

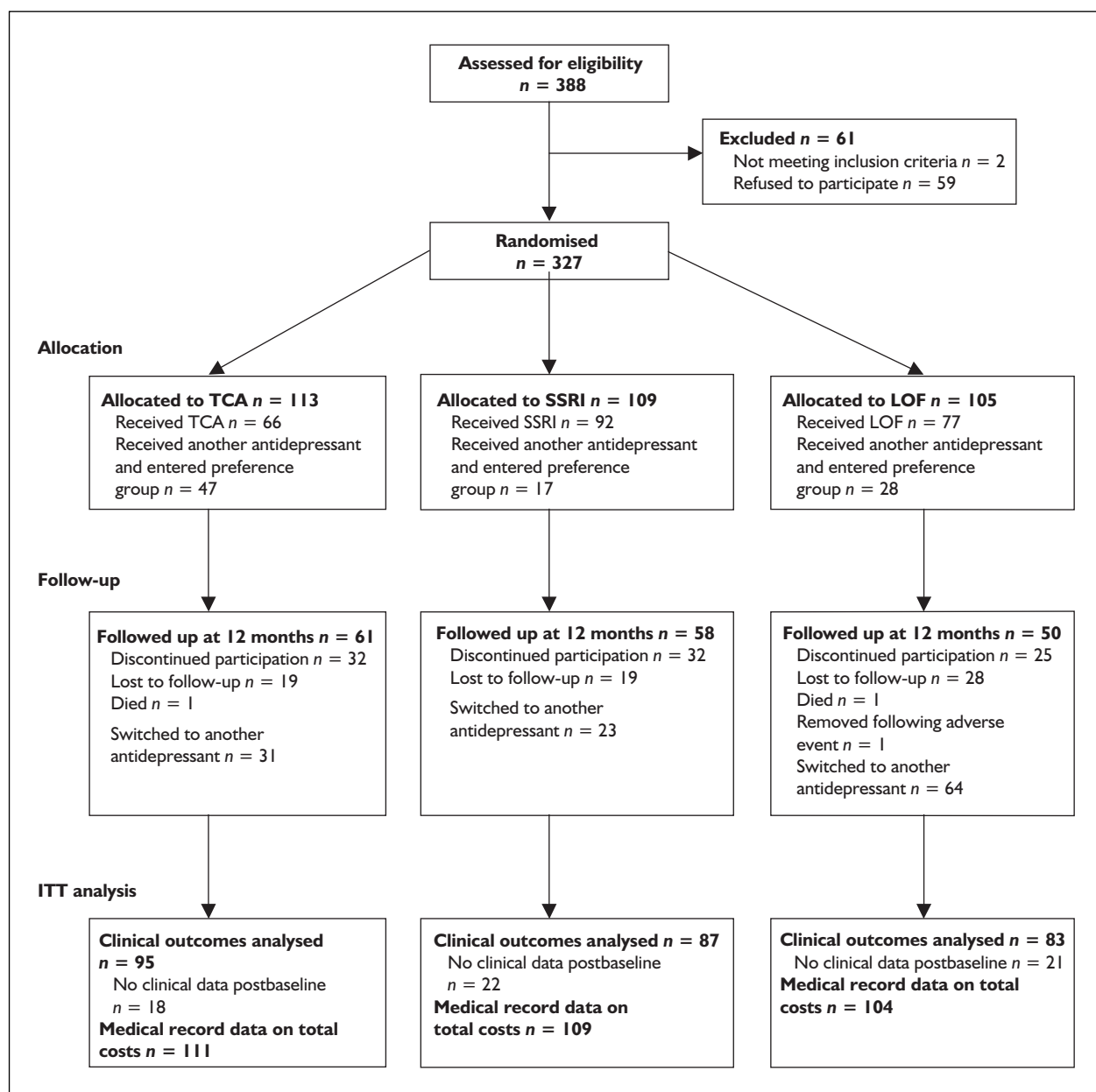


FIGURE 2 Patient flow and follow-up

TABLE 7 Academic achievement of patients

Exam level	TCA	SSRI	LOF	Total
None	33	32	24	89
NVQ1/CSE	11	10	9	30
NVQ2/GCSE	36	35	38	109
NVQ3/A level	17	14	13	44
NVQ4/HNC/HND	4	6	9	19
Degree/higher degree	8	9	8	25
Other	4	3	4	11
Total	113	109	105	327

TABLE 8 Social class of patients

Social class	TCA	SSRI	LOF	Total
I	7	7	3	17
II	21	23	30	74
III NM	30	27	22	79
III M	14	12	10	36
IV	22	24	26	72
V	6	5	6	17
Never worked	1		1	2
Married student			1	1
Not applicable because in armed forces	1		1	2
Not applicable for other reasons			2	2
Unmarried student, father's data missing	1	1		2
Missing	10	10	3	23
Total	113	109	105	327

randomised sample (327 patients, 67.0% women, 33.0% men) did not differ, nor did the mean age (43.1 years) or age range (17–91 years).

The randomised sample of 327 patients comprised 109 patients allocated to SSRI, 113 to TCA and 105 to LOF. Similar proportions of men and women were seen in all three treatment arms. The mean age was similar in the three groups, as were the age range and interquartile age range. Generally similar proportions of patients were distributed across age bands, although there were fewer elderly patients (aged 60 years or more) randomised to treatment with LOF (six patients, 4.8%) than to SSRI (17, 15.6%) or TCA (19, 16.8%).

These three groups were similar with respect to academic achievement (Table 7), social class (Table 8), economic position, marital status and ethnicity (Table 9).

Clinical characteristics at baseline

Psychiatric diagnosis

The ICD-10 diagnoses generated by interview with the CIS-R in the sample of randomised patients

are shown in Table 10. No psychiatric diagnosis was identifiable in 46 patients (14.1%).

CIS-R total score and symptom domains

The total CIS-R score was similar in all three treatment groups (SSRI, 23.83; TCA, 23.63; LOF, 23.74), as was the distribution of this score across the 15 identified symptom domains (Table 11).

Hospital anxiety and depression scale scores

The HADS scores in the three treatment groups are shown in Table 12. The mean score on both the depression subscale and the anxiety subscale was similar in all three groups, as was the distribution of patients in the three categories (no depression, possible depression and probable depression).

SF-36 scores and EQ-5D scores

The mean scores on the identified SF-36 domains did not differ statistically across the three groups at the baseline assessment. Similar proportions of patients reported difficulties on most of the five items of the EQ-5D, although there were substantially fewer patients who described problems in self-care in those randomised to SSRI treatment

TABLE 9 Economic position, marital status and ethnicity of patients

	TCA	SSRI	LOF	Total
Economic position				
Full-time employment	39	45	50	134
Part-time employment	30	20	15	65
Permanently sick/disabled	4	5	7	16
Unemployed	9	9	7	25
Retired	11	14	6	31
Student	2	2	2	6
Housewife	14	12	13	39
Other	1		2	3
Missing	3	2	3	8
Total	113	109	105	327
Marital status				
Married	58	49	47	154
Cohabiting	10	13	11	34
Widowed	6	7	7	20
Separated	8	10	5	23
Divorced	9	7	14	30
Single	20	21	18	59
Missing	2	2	3	7
Total	113	109	105	327
Ethnicity				
White	111	108	103	322
Black Caribbean			1	1
Chinese	1			1
Other Asian group	1			1
Missing		1	1	2
Total	113	109	105	327

TABLE 10 CIS-R-generated ICD-10 diagnoses at baseline

	Primary	Secondary
ICD-10 psychiatric diagnosis		
Mixed anxiety and depressive disorder	123 (37.6%)	
Moderate depressive episode	50 (15.3%)	–
Severe depressive episode	45 (13.8%)	–
Mild depressive episode	21 (6.4%)	–
Panic disorder	13 (4.0%)	9 (2.8%)
Agoraphobia	13 (4.0%)	13 (4.0%)
Social phobia	12 (3.7%)	12 (3.7%)
Obsessive–compulsive disorder	–	4 (1.2%)
Specific (isolated) phobia	–	5 (1.5%)
No identifiable psychiatric diagnosis	46 (14.1%)	–

(3%) than in those allocated to treatment with TCA treatment (13%) or treatment with LOF (9%).

Treatment ‘acceptors’ compared with the preference group

Before randomisation, patients and GPs were able to state a preference. In a substantial proportion

($n = 92$, 28.1%) of the 327 randomised patients, the GP or the patient (or both) preferred an alternative antidepressant drug to that allocated. This proportion varied between the three treatment groups: there were 66 (58.4%) acceptors and 47 (41.6%) preference patients with TCAs, 92 (84.4%) acceptors and 17 (15.6%) preference patients with SSRIs, and 77 (73.3%) acceptors and 28 (26.7%) preference patients with LOF

TABLE 11 Mean (SD) scores on CIS-R domains at baseline assessment

	TCA (n = 113)	SSRI (n = 109)	LOF (n = 105)	All (n = 327)
CIS-R domain				
Depression	2.24 (1.34)	2.38 (1.31)	2.33 (1.38)	2.31 (1.34)
Depressive ideas	3.08 (1.33)	2.88 (1.33)	3.07 (1.19)	3.01 (1.29)
Sleep problems	2.19 (1.31)	2.10 (1.30)	1.99 (1.47)	2.10 (1.36)
Irritability	1.96 (1.40)	2.07 (1.46)	2.05 (1.48)	2.02 (1.44)
Worry over physical health	0.91 (1.21)	0.82 (1.16)	0.97 (1.24)	0.90 (1.20)
Somatic symptoms	1.23 (1.34)	1.30 (1.31)	1.35 (1.36)	1.29 (1.33)
Fatigue	2.65 (1.35)	2.86 (1.20)	2.89 (1.24)	2.80 (1.27)
Poor concentration	1.90 (1.42)	1.94 (1.42)	1.96 (1.41)	1.94 (1.41)
Worry	2.29 (1.40)	2.35 (1.35)	2.15 (1.49)	2.26 (1.41)
Anxiety	2.06 (1.63)	2.10 (1.54)	2.15 (1.56)	2.10 (1.57)
Phobias	0.91 (1.31)	0.82 (1.13)	0.85 (1.14)	0.86 (1.19)
Panic	1.26 (1.46)	1.01 (1.36)	0.99 (1.35)	1.09 (1.39)
Compulsions	0.57 (1.10)	0.66 (1.10)	0.55 (1.00)	0.59 (1.06)
Obsessions	1.33 (1.64)	1.11 (1.55)	1.25 (1.60)	1.23 (1.60)
Alcohol misuse	2.84 (2.27)	2.85 (1.98)	2.55 (2.19)	2.75 (2.15)
Total	23.63 (11.21)	23.83 (9.70)	23.74 (10.96)	23.73 (10.61)

TABLE 12 Baseline HAD-D and HAD-A scores

	TCA	SSRI	LOF
Total HAD-D scores			
No depression (0–7)	25 (22%)	21 (19%)	18 (18%)
Possible depression (8–10)	35 (31%)	36 (33%)	29 (29%)
Probable depression (11–21)	52 (46%)	51 (47%)	53 (53%)
Total	112	108	100
Total HAD-A scores			
No anxiety (0–7)	8 (7%)	8 (7%)	4 (4%)
Possible anxiety (8–10)	16 (14%)	19 (18%)	22 (22%)
Probable anxiety (11–21)	88 (79%)	81 (75%)	74 (74%)
Total	112	108	100
Missing/incomplete HADS	1	1	5

TABLE 13 Numbers and percentages of patients expressing a preference

Preference	TCA	SSRI	LOF	All
Yes	12 (11%)	14 (13%)	15 (14%)	41 (13%)
No	101 (89%)	95 (87%)	90 (86%)	286 (87%)
Total	113 (100%)	109 (100%)	105 (100%)	327 (100%)

($\chi^2 = 18.7$, $df = 2$, $p < 0.001$). Patient preferences are shown in *Table 13*.

Most of the preference patients in the TCA group (30 out of 47 patients, 63.8%) commenced treatment with an SSRI. This was also the case in preference patients in both the SSRI and the LOF treatment groups. In the SSRI group, the most commonly prescribed initial treatment (11 out of 17 patients, 64.7%) in preference patients was citalopram, another SSRI antidepressant; in the

LOF group, 21 out of 28 patients (75.0%) commenced treatment with an SSRI.

Comparison of gender and age in acceptors and preference patients

The acceptor and preference patients did not differ significantly in their baseline demographic characteristics (*Table 14*). The proportion of men and women in acceptor and preference subsamples was approximately similar in all three treatment groups (χ^2 with Yates' correction): TCA,

TABLE 14 Gender and age distribution of acceptor and preference patients

	TCA (n = 113)		SSRI (n = 109)		LOF (n = 105)	
	Acceptor	Preference	Acceptor	Preference	Acceptor	Preference
Gender						
Male	22	15	36	2	21	12
Female	44	32	56	15	56	16
Total	66	47	92	17	77	28
Age (years)						
17–29	14	11	15	7	18	3
30–39	15	12	24	4	25	11
40–49	11	10	15	2	15	4
50–59	17	4	21	4	15	8
60–69	5	6	6	0	1	0
≥ 70	4	4	11	0	3	2
Totals	66	47	92	17	77	28

TABLE 15 Distribution of HADS scores for acceptor and preference patients

	TCA (n = 113)		SSRI (n = 109)		LOF (n = 105)	
	Acceptor	Preference	Acceptor	Preference	Acceptor	Preference
HAD-D scores						
No depression (0–7)	15	10	18	3	13	5
Possible depression (8–10)	20	15	30	6	35	7
Probable depression (11–2)	30	22	43	8	27	13
Missing	1	0	1	0	2	3
Total	66	47	92	17	77	28
HAD-A scores						
No anxiety (0–7)	7	1	7	1	2	2
Possible anxiety (8–10)	13	8	16	3	17	5
Probable anxiety (11–21)	45	38	68	13	56	18
Missing	1	0	1	0	2	3
Total	66	47	92	17	77	28

66.7% women in acceptor group, 68.1% in preference group ($p = 0.60$); SSRI, 60.9% women in acceptor group, 88.2% in preference group ($p = 0.06$); LOF, 72.7% in acceptor group, 57.1% in preference group ($p = 0.20$).

The age distribution of acceptor and preference patients within each treatment group differed. In the TCA treatment group, the proportion of patients aged 50 years or older in acceptors and preference patients was 39.4% and 29.8%, respectively. In the SSRI treatment group, this proportion was 41.3% and 23.5%, respectively, and in the LOF treatment group, 24.7% and 35.7%, respectively. The different pattern of age distribution between treatment groups may reflect knowledge of the differing pharmacological

properties of antidepressants. This observation should not be overemphasised, however, because of the small numbers of patients across the differing age bands.

Comparison of HADS scores in acceptors and preference patients

The distribution of HADS scores was similar in acceptor and preference patients in all three treatment groups (Table 15). In the TCA group, the proportion of patients with returned HAD-D scores indicating possible or probable depression (i.e. scores of ≥ 8) was 76.9% in acceptors and 78.7% in preference patients; in the SSRI group, the proportions were 80.2% and 82.4%, respectively; and with LOF, 82.7% and 80.0%, respectively. The proportion of patients with returned HAD-A

TABLE 16 Reasons for rejecting a randomly allocated antidepressant

Previous experience		Current features		Future problems	
Patient factors	n	Patient factors	n	Factor	n
Good effect of another drug	10	Type of employment	9	Potential for drowsiness	13
Side-effects of allocated drug	3	Responsibility for dependents	2		
		Advice of GP	25		
		Need more information	7		
Doctor factors	n	Medical factors	n		
Perceived poor efficacy	5	Suicide risk	6		
Perceived poor tolerability	22	Current target symptoms	8		
Concerns about drug cost	2	Medical co-morbidity	6		
		Concomitant treatment	2		

scores indicating possible or probable anxiety (scores of ≥ 8) was also similar across the treatment groups. In the TCA group, this proportion was 89.2% in acceptors and 80.7% in preference patients; in the SSRI group, 92.3% and 94.1%; and in the LOF group, 97.3% and 88.5%.

Stated reasons for not accepting allocated treatment group

As described above, a substantial proportion of the randomised patients did not start treatment with an antidepressant from the allocated treatment group. Ninety-two patients entered the preference arm.

The reasons for rejecting the allocated antidepressant varied considerably. The most common reason that GPs gave for an

unwillingness to prescribe an allocated drug was concern about the potential for inducing drowsiness ($n = 16$), followed by concern about potential cardiotoxicity ($n = 7$), either in therapeutic doses or after overdose in suicidal patients. The most common reason that patients gave for preferring an alternative antidepressant was having received doctors' advice that the randomly allocated treatment was inappropriate ($n = 25$), followed by wanting to discuss the treatment further with the GP ($n = 7$) and worry about potential drowsiness ($n = 6$). In 20 cases, no reason was given.

Table 16 shows the stated reasons for rejecting the allocated antidepressant, classified according to concerns about previous experience, current personal or clinical features, and potential future problems. In some patients, more than one reason was given.

Chapter 4

Clinical outcome results

Switching of antidepressants

In addition to patients who did not start treatment with the allocated medication, some patients were switched from one antidepressant class to another during the course of the study (Table 17).

Data on antidepressant treatment were available for 325 patients: among these, 75 (23%) changed antidepressant class once, 17 (5%) patients changed class twice, two patients three times and one patient four times. The proportion of patients who switched from the initial class to another was greater in the LOF group (40%) than in the TCA or SSRI group (27% and 22%, respectively) ($\chi^2 = 9.2$, $df = 2$, $p = 0.01$).

There were significant differences in the proportion of patients who changed treatment in the acceptor and preference group patients. Treatment switching occurred in 81 (34.5%) of 235 acceptor patients, but only in 14 (15.6%) of 90 preference patients ($\chi^2 = 10.4$, $df = 1$, $p = 0.0013$). This pattern was also seen within each treatment group: with TCAs, the proportions were 35% and 17%; with SSRIs, 23% and 6%; and with LOF, 46% and 19%. Exercising a preference regarding initial treatment was associated with a lower rate of switching

treatment to another antidepressant subsequently. Survival analysis of the proportion remaining on the initial antidepressant treatment from among the total group of randomised patients supported the finding that preference patients were significantly more likely to remain on this treatment than were acceptor patients ($\chi^2 = 1.19$, $df = 1$, $p = 0.001$). In the acceptor patients, allocation to LOF was associated with a significantly lower chance of remaining on initial treatment than was initial treatment with either a TCA or an SSRI ($\chi^2 = 9.71$, $df = 2$, $p = 0.008$).

The time of switching from the initial antidepressant to another class also varied between groups. In the group of all randomised patients, the proportion of switching patients who switched before 3 months was 56.8%. In the TCA treatment group, this proportion was 48.4% (15 of 31 patients); in the SSRI group, 65.2% (15 of 23 patients); and in the LOF group, 58.5% (24 of 41 patients).

In the subgroup of acceptor patients (Figure 3, Table 18), 50 of 81 (61.7%) patients switched antidepressant within 3 months: in the TCA treatment group, this proportion was 56.5% (13 of 23 switching patients); in the SSRI group, 63.6% (14 of 22 patients); and in the LOF group, 63.9%

TABLE 17 Number of class switches for all patients

		TCA	SSRI	LOF	All
Sample Accepted	No. of class switches				
	0	43 (65%)	70 (76%)	41 (53%)	154 (66%)
	1	16 (24%)	17 (18%)	31 (40%)	64 (27%)
	2	6 (9%)	5 (5%)	4 (5%)	15 (6%)
	3	1 (2%)	0	1 (1%)	2 (1%)
	All	66 (100%)	92 (100%)	77 (100%)	235 (100%)
Preference	0	39 (83%)	16 (94%)	21 (81%)	76 (84%)
	1	6 (13%)	0	5 (19%)	11 (12%)
	2	1 (2%)	1 (6%)	0	2 (2%)
	4	1 (2%)	0	0	1 (1%)
	All	47 (100%)	17 (100%)	26 (100%)	90 (100%)
	All	0	82 (73%)	86 (79%)	62 (60%)
1		22 (19%)	17 (16%)	36 (35%)	75 (23%)
2		7 (6%)	6 (6%)	4 (4%)	17 (5%)
3		1 (1%)	0	1 (1%)	2 (1%)
4		1 (1%)	0	0	1
All		113 (100%)	109 (100%)	103 (100%)	325 (100%)

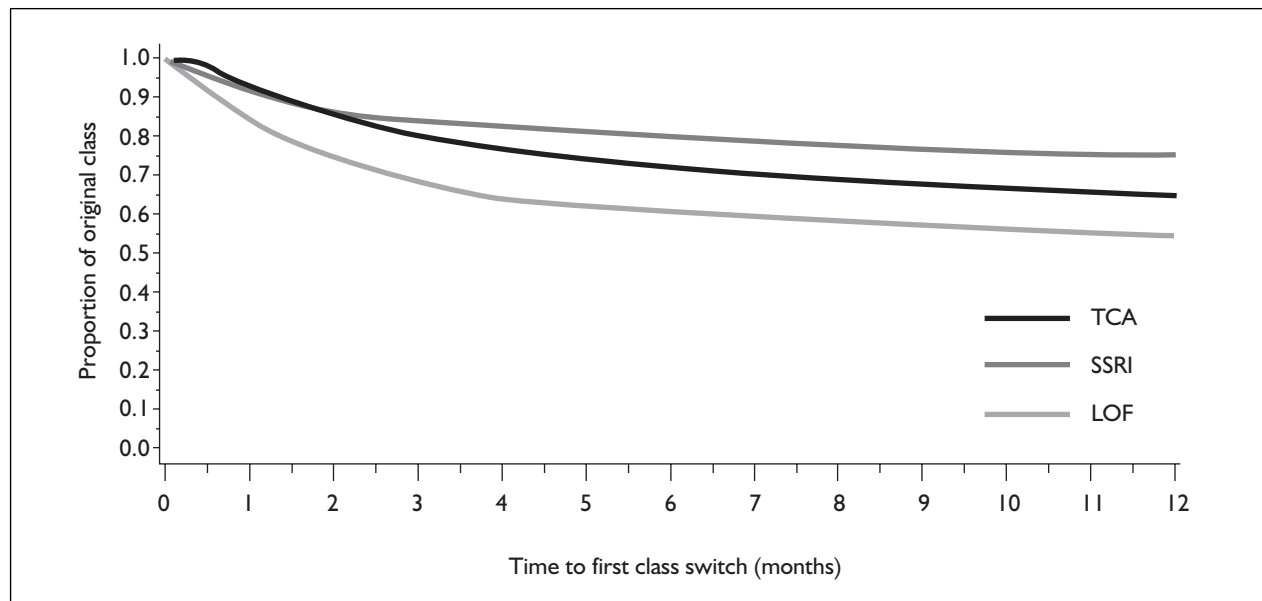


FIGURE 3 Time to first class switch for acceptors only

TABLE 18 Month of first class switch for all randomised patients

	TCA	SSRI	LOF	All
First switch before month				
All patients				
1	5 (4%)	9 (8%)	12 (11%)	26 (8%)
2	6 (5%)	5 (5%)	7 (7%)	18 (6%)
3	4 (4%)	1 (1%)	5 (5%)	10 (3%)
6	10 (9%)	6 (6%)	7 (7%)	23 (7%)
9	3 (3%)	1 (1%)	6 (6%)	10 (3%)
12	3 (3%)	1 (1%)	4 (4%)	8 (2%)
Did not switch	82 (73%)	86 (79%)	64 (61%)	232 (71%)
Total	113 (100%)	109 (100%)	105 (100%)	327 (100%)
Acceptors only				
1	4 (6%)	8 (9%)	11 (14%)	23 (10%)
2	5 (8%)	5 (5%)	7 (9%)	17 (7%)
3	4 (6%)	1 (1%)	5 (6%)	10 (4%)
6	5 (8%)	6 (7%)	6 (8%)	17 (7%)
9	3 (5%)	1 (1%)	4 (5%)	8 (3%)
12	2 (3%)	1 (1%)	3 (4%)	6 (3%)
Did not switch	43 (65%)	70 (76%)	41 (53%)	154 (66%)
Total	66 (100%)	92 (100%)	77 (100%)	235 (100%)

(23 of 36 patients). The small numbers mean that interpretation of this finding is difficult, but it suggests that proportionately more of those acceptor patients who do switch do so earlier with LOF or SSRIs than with TCAs.

Drug treatment prescribed

Table 19 shows, for all participants at the end of 12 months of follow-up, the number of person-years for which participants actually had treatment

prescribed with each drug, including the three classes to which patients could be randomised, and also three other classes to which some of them were switched. Clearly, SSRIs were most popular in terms of the number of prescriptions received, and resulting person-years of treatment for which data were available.

Table 20 shows the median and mean doses, with interquartile ranges (IQRs) and minimum and maximum doses, for patients who were prescribed TCAs at some point within the 12 months of the

TABLE 19 Person-years of follow-up and number of prescriptions for classes prescribed

	Antidepressant class					
	SSRI	TCA	LOF	SNRI	Tetracyclic	Modified cyclic
Person-years on treatment	81.60	32.79	23.44	4.33	0.10	0.05
No. of prescriptions	931	377	309	60	1	1

TABLE 20 Antidepressant daily dosage summary for patients prescribed TCAs during the 12-month study period

Dose (mg day ⁻¹)	Prescription class (TCA)				
	Dothiepin	Amitriptyline	Imipramine	Trimipramine	Clomipramine
Median	75.0	50.0	100.0	50.0	37.5
Mean	87.4	61.4	82.5	50.0	37.5
IQR (lower)	50	25	75	50	25
IQR (upper)	150	75	100	50	50
Min.	12.5	10.0	25.0	50.0	25.0
Max.	225	150	100	50	50
No. of prescriptions with daily dose available	187	111	10	3	2
No. of prescriptions without daily dose available	17	35	2	9	1

study period. It can be seen from this table that, as well as amitriptyline, dothiepin and imipramine, some patients were prescribed trimipramine and clomipramine during the course of the study. The median dose prescribed of amitriptyline of 50 mg per day is low, compared with recommended doses of 125–150 mg daily. Dothiepin has a similar recommended daily dosage, and the median dose is 75 mg which, while somewhat higher, is still low. The median daily dose of 100 mg of imipramine is higher, but the recommended daily dose for this is 150–200 mg per day. The median daily dose of 50 mg of trimipramine is also low compared to recommended doses of 150–300 mg per day. The recommended daily dose of clomipramine is anything from 30 to 150 mg daily, and the median dose prescribed in the study of 37.5 mg is clearly low when compared with this range.

It should be noted that TCAs are usually titrated upwards from a low dose, and therefore the median daily dose prescribed will in part reflect those prescriptions for lower doses given during the titration period. The maximum doses of TCA prescribed can be seen to be higher and within the therapeutic ranges for dothiepin, amitriptyline and imipramine. The maximum doses reached for trimipramine and clomipramine are still low, but the numbers of prescriptions for these drugs are very small.

Table 21 shows that the median daily doses prescribed for fluoxetine, paroxetine and citalopram were all in the recommended therapeutic range of 20–60 mg. The median dose of sertraline was at the lower end of the recommended range of 50–200 mg daily. It is perhaps not surprising that the median doses fall in these ranges for the SSRIs, as less titration is needed from the starting dose. Indeed, these drugs are often started at therapeutic dose levels. It can be seen that some prescriptions were for 10 mg of fluoxetine and paroxetine, 5 mg of citalopram and 25 mg of sertraline. Citalopram, although not included in the original list of SSRIs in the design of the study, was used relatively frequently compared with fluoxetine, paroxetine, and sertraline, which were recommended.

Table 22 shows that the median daily dose of lofepramine was 140 mg. Lofepramine is usually titrated up from 70 to 210 mg per day. Most patients were taking 140 mg per day, as can be seen from the interquartile range.

Analysis of clinical outcome

Table 23 shows the number of patients completing clinical outcome measures at each time-point through the 12 months of follow-up. Of the 268

TABLE 21 Antidepressant daily dosage summary for patients prescribed SSRIs during the 12-month study period

Dose (mg day ⁻¹)	Prescription class (SSRI)			
	Fluoxetine	Paroxetine	Citalopram	Sertraline
Median	20.0	20.0	20.0	50.0
Mean	20.7	21.6	19.4	66.1
IQR (lower)	20	20	20	50
IQR (upper)	20	20	20	100
Min.	10.0	10.0	5.0	25.0
Max.	60	40	60	100
No. of prescriptions with daily dose available	347	225	177	135
No. of prescriptions without daily dose available	21	13	7	5

TABLE 22 Antidepressant daily dosage summary for patients prescribed lofepramine during the 12-month study period

Dose (mg day ⁻¹)	Prescription class (LOF)
Median	140.0
Mean	132.6
IQR (lower)	140
IQR(upper)	140
Min.	20.0
Max.	210
No. of prescriptions with daily dose available	291
No. of prescriptions without daily dose available	18

TABLE 23 Number of patients completing clinical outcome measures at each time-point

	TCA	SSRI	LOF	All
Month				
0	113	109	105	327
1	95	87	84	266
2	89	84	81	254
3	90	82	82	254
6	70	71	62	203
9	65	63	60	188
12	62	58	51	171
Any postbaseline	95	87	86	268

patients who completed any follow-up postbaseline, all but two completed the HADs questionnaire.

Main outcome measure: HAD-D

Table 24 shows HAD-D scores for patients in the three arms of the trial, at each follow-up point over the 12 months. The table shows results for all patients randomised to the three arms, regardless of whether they accepted the treatment or started something else, in the top half of the table. The bottom half of the table shows scores for those who accepted the randomised treatment and started on it, but who may have switched treatment later, as shown above (section 'Switching of antidepressants', p. 35).

Figure 4 shows these HAD-D scores for all patients randomised, in the form of boxplots. It can be seen that the HAD-D scores fell over the 12 months in all three groups, with the largest part of the fall occurring in the first 3 months after randomisation. The results were very similar for the analysis including only those patients who accepted the randomised treatment.

Table 25 shows the HAD-D score results in terms of the proportions of patients in each group remaining not depressed and depressed at each time-point through the study.

It can be seen from Table 25 that, at 12 months, 18% of patients randomised to TCA remained depressed (HAD-D score of ≥ 8 , possible major depression), compared with 26% in the SSRI group, and 28% in the LOF group. The proportions for acceptors only are very similar. At the higher cut-off of a HAD-D score of 11 or above (probable major depression), the respective figures are 3%, 7% and 16% for TCA, SSRI and LOF.

Figure 5 shows that the proportion of patients remaining depressed in each arm fell by similar amounts over the 12-month period of follow-up, with the greatest fall in the first 3 months, and these differences are not significant (see below).

TABLE 24 HAD-D scores

		HAD-D score, including interpolated scores																				
		TCA						SSRI						LOF								
Month		0	1	2	3	6	9	12	0	1	2	3	6	9	12	0	1	2	3	6	9	12
All patients	Mean	10.4	8.8	6.9	6.0	5.0	4.7	3.8	10.5	8.6	7.0	6.4	4.6	4.3	4.3	10.5	9.0	7.8	7.0	5.2	4.8	5.0
	SD	4.1	4.1	3.9	4.2	4.4	4.0	3.3	3.6	3.8	4.2	4.4	3.6	3.7	3.9	3.9	3.7	3.7	4.1	3.8	3.9	4.7
	n	113	95	89	86	69	65	61	109	87	84	79	71	63	58	102	84	81	78	62	60	50
Acceptors only	Mean	10.5	8.8	7.3	6.3	4.6	4.7	3.6	10.6	8.6	7.1	6.5	4.6	4.3	4.5	10.4	8.9	7.9	7.0	5.2	4.8	5.1
	SD	4.0	4.0	3.4	4.1	4.1	4.2	3.6	3.5	3.7	4.2	4.4	3.6	3.8	3.9	3.8	3.7	3.6	4.2	3.7	3.8	4.5
	n	66	58	54	53	43	43	41	92	75	73	68	61	53	50	77	63	60	57	45	43	35

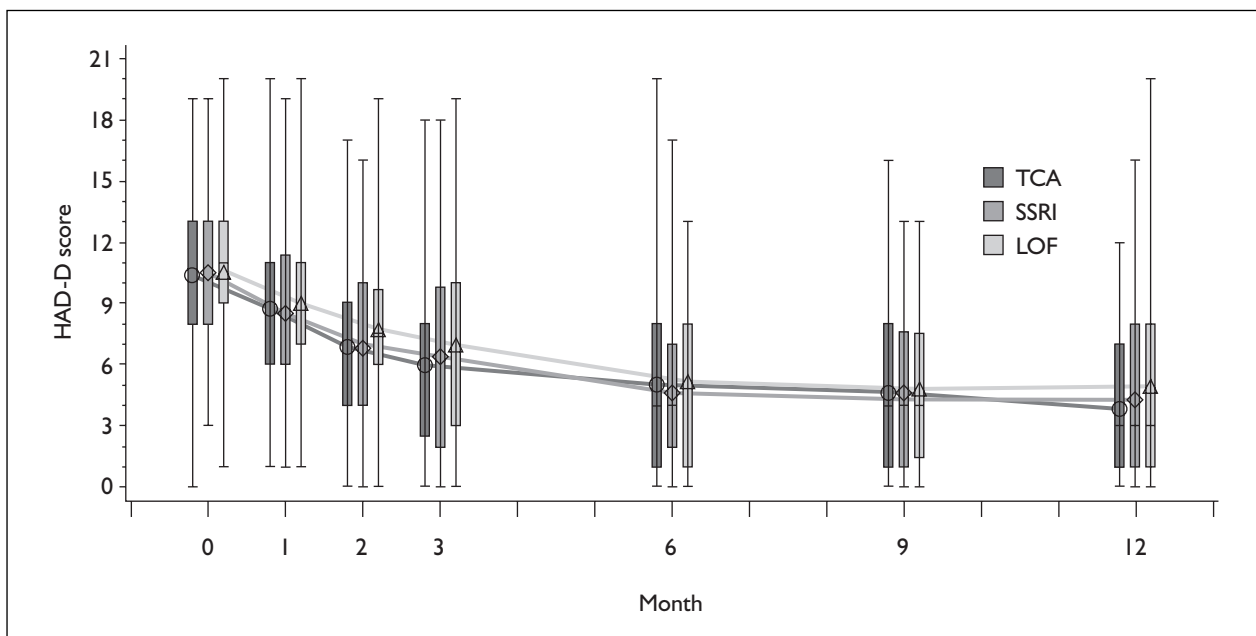


FIGURE 4 Graph of HAD-D scores for all patients

The results including only those who accepted the allocation were very similar.

Main outcome analysis: depression-free weeks

Table 26 shows the main outcome measure, that is, the number of depression-free weeks, for the patients randomised to each of the three arms, showing figures for all patients randomised, and separate figures including only those who accepted the randomisation. It can be seen from this table that the mean number of depression-free weeks observed per patient was around 26. A Kruskal-Wallis (KW) test for the difference between the groups showed no statistically significant differences ($\chi^2 = 2.23$, $df = 2$, $p = 0.327$). These figures are represented graphically as boxplots in Figure 6.

A repeated-measures ANOVA was carried out to test the significance of any differences between groups in the number of depression-free weeks, while adjusting for baseline HAD-D score. This analysis assumed that missing data were MAR (see Chapter 2, section ‘Statistical analysis’, p. 22) and uses all the available data to inform estimates of the number of depression-free weeks expected if all patients with postbaseline HAD-D scores had completed all 12 months of follow-up.

Table 27(a) shows that the mean number of depression-free weeks over a full 12 months of follow-up, estimated in this way, would be around 35.5. Furthermore, Table 27(a) and (b) shows that there were no differences found in this analysis between groups, whether including all patients randomised to the three groups regardless of

TABLE 25 Proportions of patients not depressed and depressed

HAD-D score, including interpolated scores:	Month:	Proportion of patients																																			
		TCA												SSRI												LOF											
		0	1	2	3	6	9	12	0	1	2	3	6	9	12	0	1	2	3	6	9	12															
≤ 8	All patients	%	22%	39%	55%	65%	71%	71%	82%	19%	44%	61%	62%	80%	76%	74%	19%	32%	53%	54%	74%	75%	72%														
	n	25	37	49	56	49	46	50	21	38	51	49	57	48	43	19	27	43	42	46	45	36															
≥ 8	Acceptors only	%	23%	38%	54%	64%	72%	70%	80%	20%	44%	58%	62%	80%	75%	74%	18%	32%	53%	54%	78%	77%	71%														
	n	15	22	29	34	31	30	33	18	33	42	42	49	40	37	14	20	32	31	35	33	25															
≥ 8	All patients	%	78%	61%	45%	35%	29%	29%	18%	81%	56%	39%	38%	20%	24%	26%	81%	68%	47%	46%	26%	25%	28%														
	n	88	58	40	30	20	19	11	88	49	33	30	14	15	15	83	57	38	36	16	15	14															
≥ 11	Acceptors only	%	77%	62%	46%	36%	28%	30%	20%	80%	56%	42%	38%	20%	25%	26%	82%	68%	47%	46%	22%	23%	29%														
	n	51	36	25	19	12	13	8	74	42	31	26	12	13	13	63	43	28	26	10	10	10															
≥ 11	All patients	%	47%	33%	15%	10%	9%	6%	3%	48%	34%	20%	20%	4%	3%	7%	52%	27%	21%	19%	10%	12%	16%														
	n	53	31	13	9	6	4	2	52	30	17	16	3	2	4	53	23	17	15	6	7	8															
≥ 11	Acceptors only	%	47%	31%	13%	9%	7%	5%	48%	36%	21%	22%	5%	4%	8%	52%	24%	20%	21%	9%	12%	17%															
	n	31	18	7	5	3	3	2	44	27	15	15	3	2	4	40	15	12	12	4	5	6															

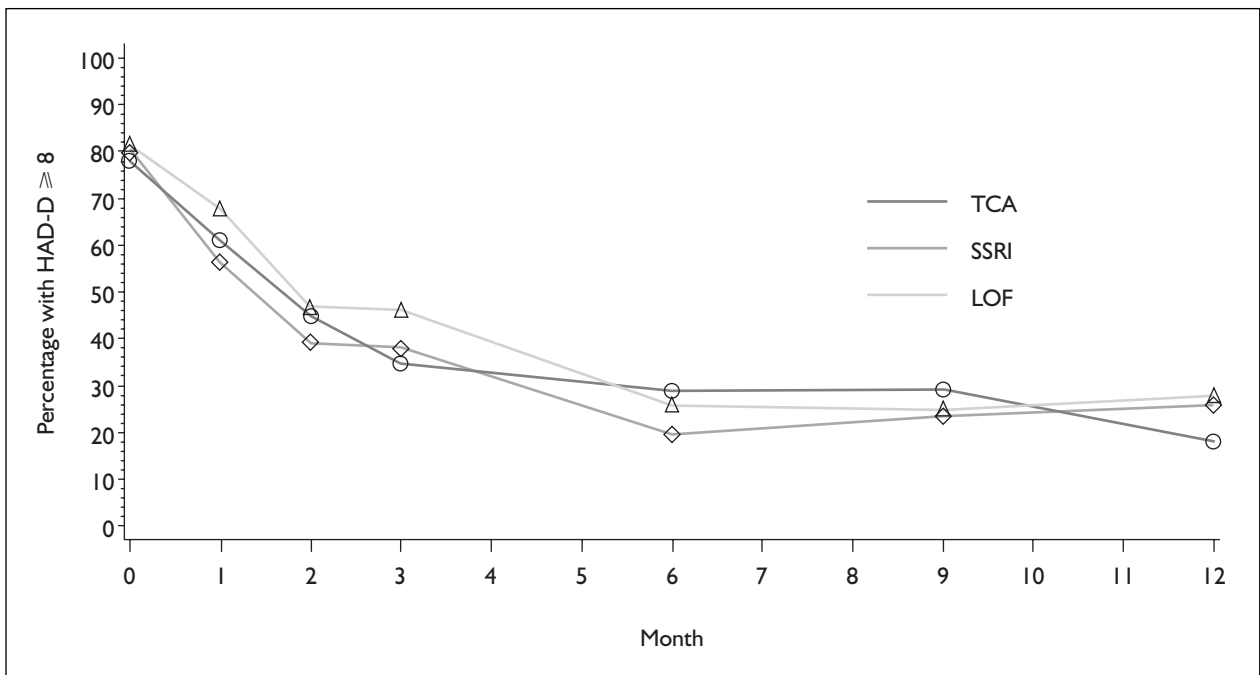


FIGURE 5 Graph showing proportions depressed at all time-points and for all patients

TABLE 26 Main outcome measure: number of depression-free weeks

	Depression-free weeks (HAD-D cut-off of 8)			
	TCA	SSRI	LOF	All
All patients				
Mean	25.3	28.3	24.4	26.0
Median	26.9	31.5	26.0	28.0
SD	19.3	18.7	19.3	19.1
IQR (lower)	6	10	5	6
IQR (upper)	45	46	45	45
Min.	0	0	0	0
Max.	52	52	52	52
n	95	87	83	265
Acceptors only				
Mean	25.9	27.8	23.9	26.0
Median	32.7	30.8	24.2	30.4
SD	19.0	18.6	19.6	19.0
IQR (lower)	6	10	5	6
IQR (upper)	44	46	44	45
Min.	0	0	0	0
Max.	52	52	52	52
n	58	75	63	196

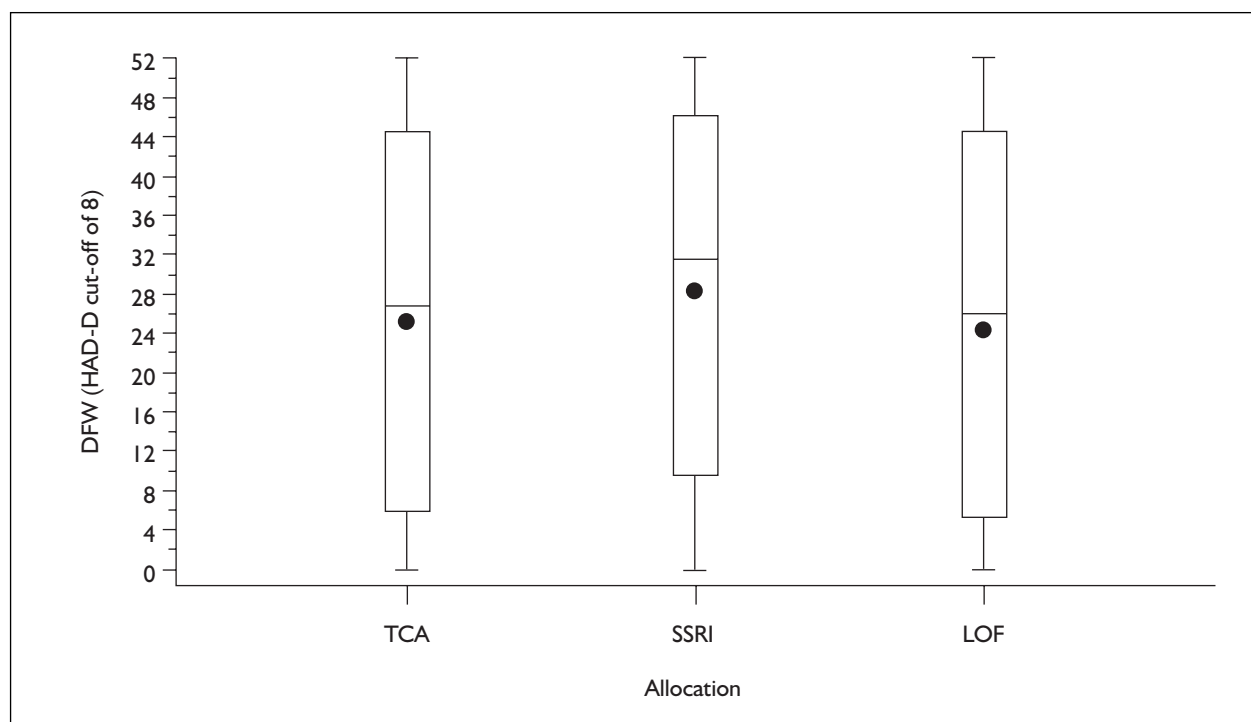


FIGURE 6 At last postbaseline HAD-D assessment: boxplot of number of depression-free weeks

TABLE 27 At 12 months: number of depression-free weeks estimated by repeated-measures ANOVA (HAD-D cut-off of 8) for (a) all patients and (b) acceptors only

Allocation	Patients	Difference	Depression-free weeks (HAD-D cut-off of 8)		
			Mean	SE	95% CI
(a) All patients					
TCA	95		35.5	1.8	31.9 to 39.1
SSRI	87		36.6	1.9	32.9 to 40.3
LOF	84		34.8	1.9	31.0 to 38.7
		SSRI – TCA	1.1	2.6	–4.0 to 6.3
		TCA – LOF	0.7	2.7	–4.6 to 5.9
		SSRI – LOF	1.8	2.7	–3.5 to 7.1
(b) Acceptors only					
TCA	58		34.5	2.3	30.0 to 39.0
SSRI	75		36.4	2.0	32.4 to 40.3
LOF	63		35.0	2.2	30.6 to 39.5
		SSRI – TCA	1.9	3.0	–4.1 to 7.9
		TCA – LOF	–0.5	3.2	–6.9 to 5.8
		SSRI – LOF	1.4	3.0	–4.6 to 7.3

whether they actually started on the treatment, or including only those who agreed to start the allocated treatment. It can be seen that the mean difference between groups is relatively small (SSRI minus TCA 1.1, TCA minus LOF 0.7, and SSRI minus LOF 1.8), but the 95% confidence intervals are wide. Results are similar for the comparison including only those who accepted the allocated drug, where the confidence intervals are also wide.

A repeated-measures ANOVA of depression-free weeks, using the higher HAD-D cut-off of 11 (probable major depression), and adjusted for baseline HAD-D score, is shown in *Table 28*. Again, the main finding is that there is no significant difference between the groups in the mean number of depression-free weeks, whether including all the patients randomised to the three arms, or including only those who accepted the allocated treatment.

TABLE 28 At 12 months: number of depression-free weeks estimated by repeated-measures ANOVA (HAD-D cut off of 11) for (a) all patients and (b) acceptors only

Allocation	Patients	Difference	Depression-free weeks (HAD-D cut-off of 11)		
			Mean	SE	95% CI
(a) All patients					
TCA	95		45.5	1.1	43.3 to 47.7
SSRI	87		44.8	1.1	42.6 to 47.1
LOF	84		43.5	1.2	41.1 to 45.9
		SSRI – TCA	–0.7	1.6	–3.8 to 2.5
		TCA – LOF	2.0	1.6	–1.2 to 5.2
		SSRI – LOF	1.3	1.7	–1.9 to 4.6
(b) Acceptors only					
TCA	58		45.3	1.4	42.5 to 48.2
SSRI	75		44.7	1.3	42.3 to 47.2
LOF	63		43.1	1.4	40.2 to 45.9
		SSRI – TCA	–0.6	1.9	–4.4 to 3.2
		TCA – LOF	2.3	2.0	–1.8 to 6.3
		SSRI – LOF	1.7	1.9	–2.1 to 5.5

TABLE 29 Total CIS-R scores at all time-points for (a) all patients and (b) acceptors only

Month:	Total CIS-R scores														
	TCA					SSRI					LOF				
	0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
(a) All patients															
Mean	23.63	11.86	9.28	7.51	7.71	23.83	13.70	10.37	11.34	8.33	23.74	12.12	10.03	7.63	8.69
SD	11.21	10.09	10.38	9.12	8.72	9.70	11.39	10.56	11.62	9.58	10.96	10.15	10.13	8.33	11.37
IQR (lower)	16	3	1	1	2	17	4	2	2	1	14	5	0	0	1
IQR (upper)	31	18	15	12	12	31	22	14	14	13	33	18	19	13	13
n	113	81	43	35	38	109	76	46	41	36	105	74	34	30	26
(b) Acceptors only															
Mean	22.27	11.46	9.17	7.77	8.17	23.47	13.30	9.95	10.30	7.87	24.88	12.00	10.65	8.21	7.59
SD	10.67	9.87	10.23	10.22	10.36	9.30	11.14	10.37	11.86	8.85	11.01	10.15	10.43	8.63	8.90
IQR (lower)	14	3	1	1	1	17	4	2	2	0	15	5	0	0	1
IQR (upper)	29	18	13	14	14	31	22	14	12	13	33	17	19	14	13
n	66	50	29	22	24	92	64	39	33	30	77	56	26	24	17

Secondary outcome measure: CIS-R

Total symptom scores on the CIS-R fell in all groups to a similar extent across the 12 months of follow-up (Table 29). Mean scores at baseline were around 24 in each group, and they fell to around 8 at 12 months, whether including all patients randomised to the treatments, or only those who accepted the allocated treatment.

Table 30 shows CIS-R scores on the depression subscale. It can be seen that scores of around 2.3 at baseline fell in all three groups over the 12 months.

Table 31 shows similar falls from around 3.0 at baseline in all three groups for the CIS-R dimension of depressive ideas.

Scores on the other CIS-R subscales of somatic symptoms, fatigue, poor concentration, sleep problems, irritability, worry over physical health, worry, anxiety, phobias, panic, compulsions and obsessions all fell between baseline and 12 months in all three groups to a roughly similar extent. Alcohol misuse scores were generally low and stayed so throughout the 12 months of the trial.

TABLE 30 CIS-R scores for the depression dimension for (a) all patients and (b) acceptors only

		CIS-R depression dimension scores														
		TCA					SSRI					LOF				
Month:		0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
(a) All patients																
Mean		2.24	0.74	0.72	0.49	0.39	2.38	0.92	0.65	0.71	0.37	2.33	0.89	0.82	0.60	0.77
SD		1.34	1.03	1.22	0.89	0.89	1.31	1.21	1.04	1.19	0.69	1.38	1.11	1.16	0.97	1.34
IQR (lower)		1	0	0	0	0	1	0	0	0	0	1	0	0	0	0
IQR (upper)		3	1	1	1	0	4	2	1	1	1	4	2	2	1	1
n		112	80	43	35	38	109	76	46	41	35	104	73	33	30	26
(b) Acceptors only																
Mean		2.22	0.78	0.76	0.50	0.46	2.38	0.94	0.67	0.70	0.34	2.42	0.80	0.84	0.71	0.71
SD		1.34	1.10	1.18	0.96	1.02	1.25	1.26	1.11	1.21	0.55	1.40	1.07	1.18	1.04	1.10
IQR (lower)		1	0	0	0	0	1	0	0	0	0	1	0	0	0	0
IQR (upper)		3	1	1	1	0	3	2	1	1	1	4	2	2	1	1
n		65	49	29	22	24	92	64	39	33	29	76	56	25	24	17

TABLE 31 CIS-R scores for the depressive ideas dimension for (a) all patients and (b) acceptors only

		CIS-R depressive ideas dimension scores														
		TCA					SSRI					LOF				
Month:		0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
(a) All patients																
Mean		3.08	2.47	2.29	2.30	2.50	2.88	2.56	2.28	2.36	1.80	3.07	2.14	2.31	1.36	2.75
SD		1.33	1.38	1.49	0.82	0.93	1.33	1.50	1.56	1.15	1.48	1.19	1.33	1.03	1.03	1.58
IQR (lower)		2	2	1	2	2	2	2	1	2	1	3	1	2	1	2
IQR (upper)		4	4	3	3	3	4	4	4	3	3	4	3	3	2	4
n		97	36	14	10	8	99	36	18	14	10	89	36	13	11	8
(b) Acceptors only																
Mean		3.00	2.32	2.00	2.33	2.80	2.81	2.43	2.07	2.27	1.56	3.17	2.44	2.50	1.30	2.17
SD		1.20	1.46	1.55	0.82	0.84	1.34	1.55	1.59	1.19	1.33	1.20	1.08	0.85	1.06	1.33
IQR (lower)		2	1	0	2	2	2	2	1	1	1	3	2	2	1	2
IQR (upper)		4	4	3	3	3	4	4	4	3	2	4	3	3	2	3
n		57	22	11	6	5	85	30	14	11	9	66	25	10	10	6

Secondary outcome measure: SF-36

Figure 7 shows that scores on the SF-36 mental health subscale improved in all three groups, from around 37 at baseline to around 70 at 12-month follow-up, for the total sample of patients randomised, and when including only those who accepted the allocated treatment.

Figure 8 shows that role limitation due to emotional problems as measured by the SF-36 improved from mean scores of around 23 to around 75, in all three groups over the 12 months of follow-up.

Table 32 shows that the SF-36 general health perception subscale improved from scores of around 54 to around 65 in all three groups across the 12 months of follow-up.

Just as the improvement in depression symptoms took place largely in the first 3 months of follow-up, so did the improvement in SF-36 scores, although there continued to be some improvement between months 3 and 12.

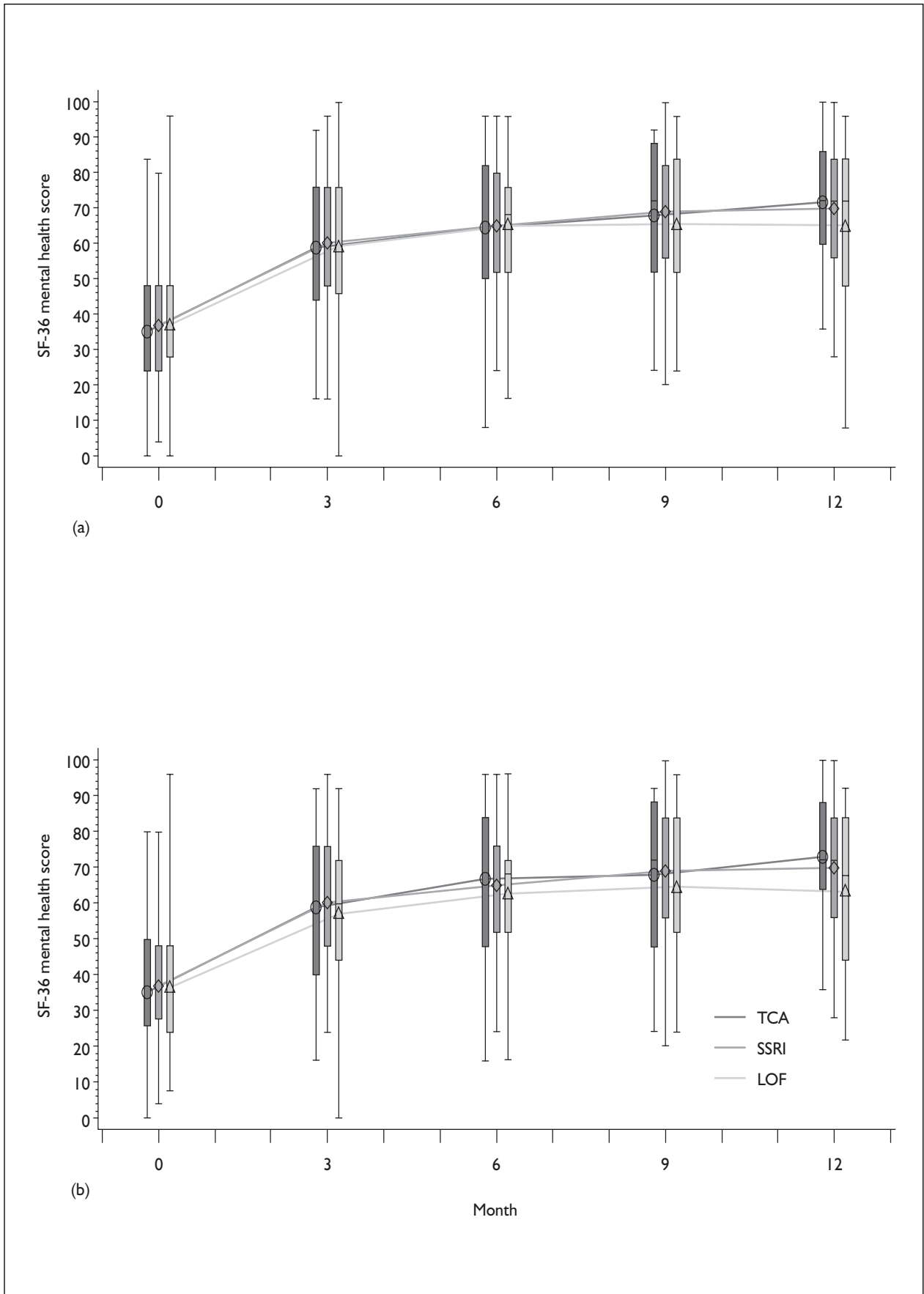


FIGURE 7 SF-36 mental health scores, for (a) all patients and (b) acceptors only

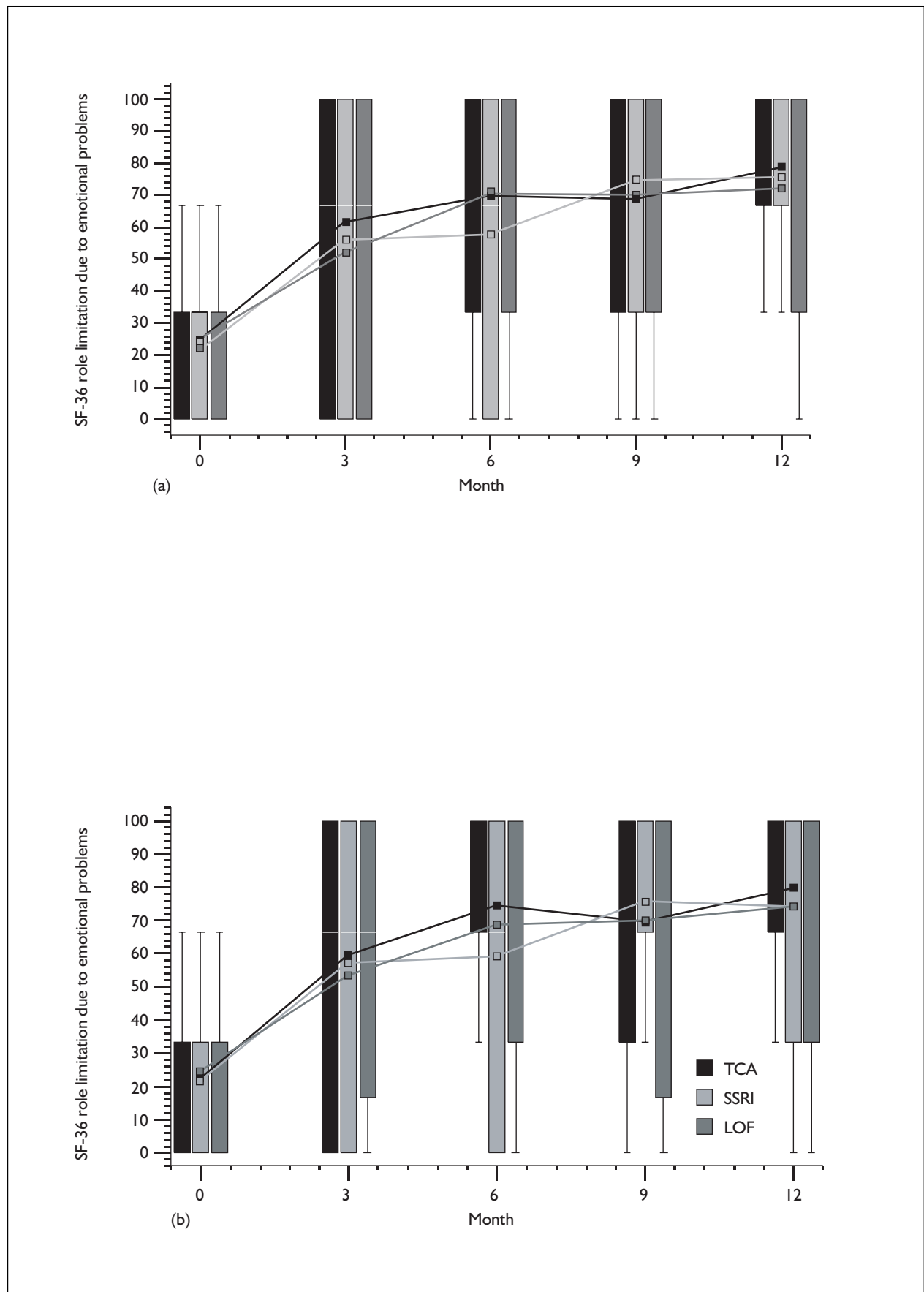


FIGURE 8 SF-36 scores for role limitation due to emotional problems, for (a) all patients and (b) acceptors only

TABLE 32 SF-36 scores on general health perception for (a) all patients and (b) acceptors only

		SF-36 general health perception scores																					
		TCA						SSRI						LOF						All			
Month:		0	3	6	9	12	0	3	6	9	12	0	3	6	9	12	0	3	6	9	12		
(a) All patients																							
Mean		56.8	65.8	65.0	67.7	67.7	52.7	59.9	65.6	64.5	66.6	53.0	57.4	65.9	67.6	61.1	54.2	61.2	65.5	66.5	65.3		
SD		22.8	21.2	23.0	21.3	22.2	21.8	22.3	19.6	23.7	23.6	22.5	25.1	22.9	23.0	25.3	22.4	23.0	21.7	22.6	23.7		
IQR (lower)		42	55	52	52	52	35	37	52	45	50	35	35	55	52	40	35	42	52	50	47		
IQR (upper)		72	82	82	87	82	67	77	82	85	87	72	77	82	82	82	72	82	82	87	82		
n		111	77	57	52	55	104	73	59	56	55	104	68	52	42	47	319	218	168	150	157		
(b) Acceptors only																							
Mean		57.9	66.6	70.2	69.2	70.2	53.5	59.6	65.9	65.8	67.1	53.5	55.9	65.3	66.2	61.1	54.8	60.5	66.9	67.0	66.4		
SD		21.7	20.7	18.9	18.8	21.3	21.5	21.2	18.6	21.9	22.8	21.8	24.8	22.5	23.0	23.5	21.6	22.5	19.9	21.1	22.6		
IQR (lower)		42	54	55	52	52	37	37	52	45	50	35	32	57	52	42	37	42	55	52	50		
IQR (upper)		72	82	82	87	82	67	77	77	82	87	67	77	82	82	80	70	77	82	85	82		
n		66	48	35	35	38	87	63	50	46	47	76	51	39	31	33	229	162	124	112	118		

Secondary outcome measure: EQ-5D

The scores on the thermometer self-rating of quality of life for the EQ-5D for the three groups over the 12 months of follow-up are shown graphically as a boxplot in *Figure 9*. It should be noted that the mean score at baseline of 49.0 was somewhat lower for the LOF group than the mean scores for the TCA group of 53.4 and for the SSRI group of 53.6. The scores in all three groups improved by around 20 points over the 12 months of follow-up, with a slighter greater improvement

in the TCA group of 22.5, compared with 23.0 in the SSRI group and 19.9 in the LOF group. Again, the main improvement in each group took place in the first 3 months of follow-up, with some further improvement over the remaining 9 months.

Tables 33–35 show the improvements in the three groups in scores on the five EQ-5D domains of anxiety and depression, walking about, self-care, performing usual activities and pain or discomfort.

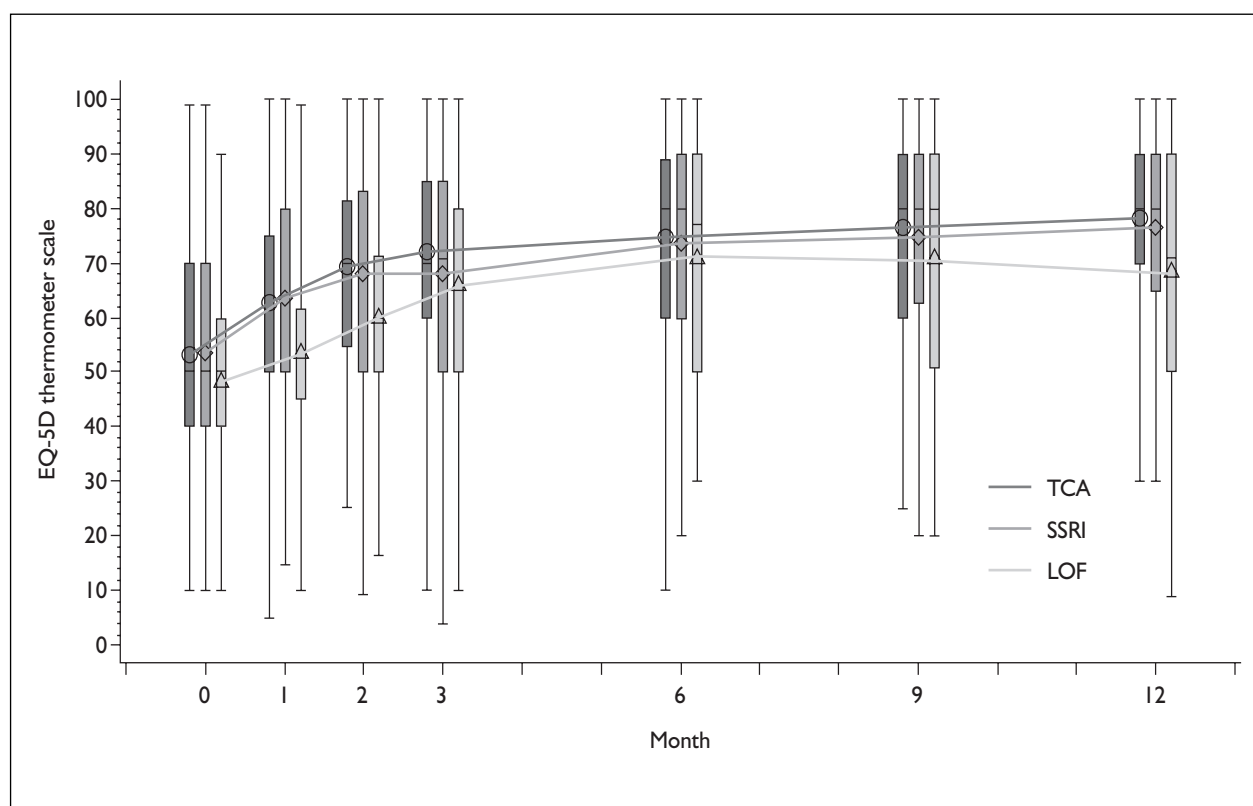


FIGURE 9 Graph of EQ-5D thermometer scale for all patients

TABLE 33 EQ-5D results for 'anxious or depressed' and 'walking about' domains

EQ-5D domain	EQ-5D results (anxious or depressed and walking about) (%)																			
	TCA						SSRI						LOF							
	0	1	2	3	6	9	0	1	2	3	6	9	0	1	2	3	6	9	12	
Anxious or depressed																				
Extremely	28	8	5	8	5	6	2	21	6	3	8	2	2	25	10	10	3	2	5	10
Acceptors only	28	6	5	4	3	6	6	21	5	2	8	2	2	28	9	9	2	3	3	9
Moderately	65	78	63	53	42	35	41	72	77	64	53	56	44	70	78	60	63	56	55	46
Acceptors only	66	77	64	60	39	33	33	71	79	64	53	59	45	65	81	67	66	62	55	54
Not anxious/depressed	7	14	32	39	53	59	58	7	17	33	39	43	54	6	12	29	34	42	41	44
Acceptors only	6	17	31	35	58	61	67	8	16	34	39	39	53	7	9	23	32	36	42	37
Walking about																				
Confined to bed																				
All patients																				
Acceptors only																				
Some problems	19	22	20	18	24	24	15	23	19	19	18	25	21	25	15	16	24	13	14	23
Acceptors only	17	17	21	19	25	22	18	25	21	20	19	28	23	24	14	16	25	15	13	29
No problems	81	78	80	82	76	76	85	77	81	81	82	75	79	75	83	84	76	87	86	77
Acceptors only	83	83	79	81	75	78	82	75	79	80	81	72	77	76	84	84	75	85	87	71

TABLE 34 EQ-5D results for 'self-care' and 'performing usual activities' domains

Allocation:	EQ-5D results (self-care and performing usual activities) (%)																				
	TCA						SSRI						LOF								
	0	1	2	3	6	9	12	0	1	2	3	6	9	12	0	1	2	3	6	9	12
EQ-5D domain																					
Self-care																					
Unable to wash or dress	1	1					1	1					1	1							
Acceptors only	2						1						2								
Some problems	12	8	7	6	8	11	8	11	8	2	3	4	10	7	10	7	9	6	6	5	6
Acceptors only	12	6	5	6	11	11	8	11	8	2	2	5	9	9	9	9	9	8	8	6	9
No problems	87	91	93	94	92	89	92	89	92	97	97	100	96	90	93	100	90	92	91	94	95
Acceptors only	86	94	95	94	89	89	92	89	92	97	98	100	95	91	91	100	91	91	92	92	89
Performing usual activities																					
Unable	4	3	2	1	5		2			4	4	3	3	2	5	2	3	2	2	2	2
Acceptors only	3	4	3	2			3			4	5	4	3	2	5	2	4	3	3	3	3
Some problems	62	59	41	36	34	37	25	37	25	60	52	38	44	37	28	32	62	55	38	49	33
Acceptors only	66	62	44	40	39	39	26	39	26	62	48	38	42	35	28	33	64	53	33	45	36
No problems	34	38	58	62	61	63	73	63	73	36	43	59	53	62	72	68	33	43	62	48	65
Acceptors only	31	34	54	58	61	61	72	61	72	34	47	58	55	63	72	67	31	44	67	51	62

TABLE 35 EQ-5D results for 'pain or discomfort' domain

		EQ-5D results (pain or discomfort) (%)																				
		TCA					SSRI					LOF										
Allocation:	Month:	0	1	2	3	6	9	12	0	1	2	3	6	9	12	0	1	2	3	6	9	12
EQ-5D domain																						
Pain or discomfort																						
Extreme pain		5	4	3	6	7	6	5	7	3	3	6	8	5	4	6	12	3	4	8	8	10
Acceptors only		6	4	5	8	8	8	8	8	3	2	5	7	4	2	4	14	2	2	8	8	11
Moderate pain		39	33	25	26	37	33	34	43	41	38	47	44	42	39	48	23	31	42	40	39	40
Acceptors only		34	26	23	21	36	31	33	44	43	40	47	44	43	39	55	23	33	43	41	42	43
No pain		56	63	71	68	56	61	61	50	57	59	47	48	53	58	46	65	66	54	52	61	50
Acceptors only		60	70	72	71	56	61	59	48	53	58	48	48	53	59	41	63	65	55	51	58	46

Chapter 5

Economic analysis

The results of the economic analysis are presented in four sections:

- analysis of total resource use and costs to 1 year from randomisation
- results of the cost-effectiveness analysis, measured in terms of cost per depression free week
- results of the cost-utility analysis, presented in terms of cost per QALY
- results from a series of sensitivity analyses.

Analysis of costs to 1 year

Patient sample

Three-hundred and twenty-seven patients were randomised in the study. GP records were not available for three of these patients: the notes of one patient had been transferred to another practice after they moved house, one patient's notes were closed and the records for the third patient were paper based and not available at the practice. Thus, the total number of observations in this analysis is 324. Resource-use information relates to a 1-year period from randomisation for each patient.

Costs and resource use

Details of all inpatient stays over the 12-month period are shown in *Table 36*. There were no statistically significant differences in the number of inpatient days between the three groups (KW $\chi^2 = 3.97$, $df = 2$, $p = 0.137$) or in the number of psychiatric-related inpatient days (KW $\chi^2 = 0.05$, $df = 2$, $p = 0.974$). There was little difference in the mean values for the TCA and SSRI groups compared with the lengths of stay calculated for the cost-effectiveness analysis below (see *Table 42*).

Table 37 details means and standard deviations for other key non-drug resource use. Overall mean levels of resource use are slightly larger measured over the full 12 months for all 324 patients than when measured to last completed outcome measure for those patients included in the cost-effectiveness or cost-utility analyses (see *Table 43*). The results of the Kruskal-Wallis test for statistically significant differences are shown in Appendix 13 (*Table 70*). There were no statistically significant differences between the three groups for any of the items.

Mean, SD and median overall costs for each of the three groups are shown in *Table 38*. The differences between the three groups in costs of non-drug service-use were not statistically significant (KW $\chi^2 = 1.44$, $df = 2$, $p = 0.486$). However, there were statistically significant differences in the costs of all prescriptions (KW $\chi^2 = 18.90$, $df = 2$, $p < 0.001$) and antidepressant prescriptions only (KW $\chi^2 = 23.58$, $df = 2$, $p < 0.001$). The mean total costs were similar for the SSRI and LOF groups, and slightly lower for the TCA group. However, these differences were not statistically significant (KW $\chi^2 = 4.78$, $df = 2$, $p = 0.092$).

Testing for equivalence of cost

The cost data measured to 12 months were used to test the hypothesis that the costs associated with each treatment strategy were equivalent. The maximum acceptable difference in costs was defined as 5% of the log mean cost of the TCA arm, in line with the sample size calculation. Thus, for this sample, to demonstrate equivalence the 95% confidence interval for the difference in log costs should exclude the range -0.332 to $+0.332$. *Table 39* shows that equivalence is not demonstrated for any of the three comparisons.

TABLE 36 Details of inpatient stay to 12 months from randomisation

	TCA (n = 111)	SSRI (n = 109)	LOF (n = 104)	All (n = 324)
Psychiatric inpatient stay (days), mean (SD)	0.56 (4.67)	0 (0)	0.09 (0.88)	0.22 (2.78)
All inpatient stay (days), mean (SD)	1.31 (5.65)	0.61 (2.76)	1.24 (7.01)	1.05 (5.40)

TABLE 37 Mean (SD) number of contacts for other key items of non-drug resource use to 12 months from randomisation

	TCA (n = 111)	SSRI (n = 109)	LOF (n = 104)	All (n = 324)
Visit to GP at surgery	8.35 (4.84)	10.10 (7.14)	8.74 (5.39)	9.08 (5.90)
Contact with GP by telephone	0.66 (1.89)	1.19 (3.07)	0.54 (1.11)	0.80 (2.20)
Home visit by GP	0.34 (1.23)	0.48 (1.51)	0.55 (2.55)	0.45 (1.84)
Contact with practice nurse at surgery	1.18 (1.73)	1.78 (2.93)	1.32 (2.09)	1.43 (2.31)
Home visit by district nurse	0.77 (6.87)	0.33 (2.30)	0.05 (0.32)	0.39 (4.24)
Contact with community psychiatric nurse	0.03 (0.16)	0.06 (0.31)	0.30 (1.99)	0.13 (0.15)
Visit to counsellor	0.21 (0.79)	0.41 (1.51)	0.36 (1.21)	0.33 (1.20)
Attendance at day centre	0.45 (3.41)	0 (0)	0.42 (3.41)	0.29 (2.78)
Attendance at non-psychiatric clinic	0.80 (1.54)	1.17 (2.33)	0.88 (1.51)	0.95 (1.84)
Contact with psychiatrist	0.18 (0.79)	0.04 (0.27)	0.17 (0.70)	0.13 (0.63)
Visit to A&E	0.12 (0.48)	0.22 (0.63)	0.20 (0.56)	0.18 (0.56)

TABLE 38 Summary of costs to 12 months from randomisation

	TCA (n = 111)	SSRI (n = 109)	LOF (n = 104)	All (n = 324)
Non-drug service use				
Mean	£646	£627	£676	£649
(SD)	(£1291)	(£1342)	(£1822)	(£1493)
Median	£256	£305	£278	£278
All prescriptions				
Mean	£116	£249	£192	£185
(SD)	(£137)	(£405)	(£301)	(£305)
Median	£66	£136	£92	£95
Of which antidepressant prescriptions				
Mean	£52	£87	£74	£71
(SD)	(£69)	(£83)	(£69)	(£75)
Median	£26	£65	£58	£48
Total costs				
Mean	£762	£875	£867	£834
(SD)	(£1336)	(£1566)	(£1907)	(£1610)
Median	£359	£503	£384	£408
95% CI ^a	£553 to £1059	£675 to £1355	£634 to £1521	£691 to £1041

^a Bootstrapped using 5000 replications.

TABLE 39 Cost data: 95% confidence intervals for differences in log costs to 12 months

	SSRI – LOF	TCA – LOF	SSRI – TCA
95% CI for difference in log cost	-0.185 to 0.373	-0.409 to 0.141	-0.050 to 0.506

Cost-effectiveness analysis

Patient sample

Two-hundred and sixty-five patients reported HADS information at baseline and at least one time-point postbaseline. Resource-use information was not available for one patient whose records were paper based and not available at the practice. Thus, the total number of observations in this cost-effectiveness analysis is 264. All data in this

section relate to the period between date of randomisation and date of last completed HADS questionnaire. *Table 40* summarises the lengths of this period for patients included in this analysis.

Outcomes (depression-free weeks)

The mean numbers of depression-free weeks for the 264 patients included in the cost-effectiveness analysis are shown in *Table 41*. The mean number

TABLE 40 Summary of length of follow-up from randomisation to date of last HADS (weeks) for patients included in the cost-effectiveness analysis

	TCA (n = 95)	SSRI (n = 87)	LOF (n = 82)	All (n = 264)
Mean	37	40	38	38
(SD)	(18)	(16)	(17)	(17)
Median	47	48	47	47

TABLE 41 Summary of depression-free weeks to date of last HADS (using cut-off of 8)

	TCA (n = 95)	SSRI (n = 87)	LOF ^b (n = 82)	All (n = 264)
Mean	25.25	28.29	24.60	26.05
(SD)	(19.32)	(18.75)	(19.33)	(19.13)
Median	26.86	31.50	26.12	28.00
95% CI ^a	21.3 to 29.0	24.3 to 32.2	20.6 to 28.9	23.9 to 28.4

^a Bootstrapped using 5000 replications.
^b Differs from Table 26 owing to the omission of one patient with missing resource-use data.

TABLE 42 Details of inpatient stay from randomisation to date of last HADS

	TCA (n = 95)	SSRI (n = 87)	LOF (n = 82)	All (n = 264)
Psychiatric inpatient stay only (days), mean (SD)	0.65 (5.05)	0 (0)	0.11 (0.99)	0.27 (3.08)
All inpatient stay (days), mean (SD)	1.35 (5.87)	0.63 (2.99)	0.44 (1.53)	0.83 (4.02)

TABLE 43 Mean (SD) number of contacts for other key items of non-drug resource use stay from randomisation to date of last HADS

	TCA (n = 95)	SSRI (n = 87)	LOF (n = 82)	All (n = 264)
Visit to GP at surgery	7.23 (5.18)	8.41 (6.72)	7.60 (5.21)	7.73 (5.74)
Contact with GP by telephone	0.67 (1.96)	1.29 (3.26)	0.40 (0.80)	0.79 (2.28)
Home visit by GP	0.28 (1.19)	0.40 (1.51)	0.22 (0.70)	0.30 (1.19)
Contact with practice nurse at surgery	0.92 (1.37)	1.51 (2.67)	1.09 (1.91)	1.16 (2.05)
Home visit by district nurse	0.89 (7.42)	0.41 (2.57)	0.05 (0.35)	0.47 (4.69)
Contact with community psychiatric nurse	0.03 (0.18)	0.06 (0.32)	0.32 (1.83)	0.13 (1.05)
Visit to counsellor	0.22 (0.81)	0.49 (1.67)	0.40 (1.31)	0.37 (1.30)
Attendance at day centre	0.53 (3.68)	0 (0)	0.54 (3.83)	0.36 (3.07)
Attendance at non-psychiatric clinic	0.72 (1.56)	1.05 (2.28)	0.76 (1.51)	0.84 (1.81)
Contact with psychiatrist	0.11 (0.66)	0.02 (0.15)	0.16 (0.58)	0.09 (0.52)
Visit to A&E	0.11 (0.45)	0.24 (0.65)	0.12 (0.33)	0.16 (0.50)

of depression-free weeks was greatest for the SSRI group, although not significantly so.

Resource use and costs

Details of inpatient stay and other non-drug resource use for these patients are shown in Tables 42 and 43. Thirty patients were admitted as inpatients during the period (ten patients in each group). Most of this inpatient stay was classed as 'non-psychiatric'. Only two patients in the TCA arm and one patient in the LOF arm were admitted for psychiatric inpatient stay. Means and

standard deviations of numbers of contacts for other items of resource use are shown in Table 43. There were no statistically significant differences between groups for any item of resource use.

A summary of the costs of patients, measured between time of randomisation and last completed HADS questionnaire, is shown in Table 44. The LOF group had the lowest costs of non-drug service use at slightly over £400, while these costs were broadly similar for the other two groups. Total drug costs were much lower for patients

TABLE 44 Summary of costs from randomisation to date of last HADS

	TCA (n = 95)	SSRI (n = 87)	LOF (n = 82)	All (n = 264)
Non-drug service use				
Mean	£612	£604	£418	£549
(SD)	(£1329)	(£1472)	(£561)	(£1202)
Median	£224	£269	£241	£236
All prescriptions				
Mean	£99	£206	£175	£158
(SD)	(£135)	(£315)	(£255)	(£247)
Median	£53	£110	£88	£78
Of which antidepressant prescriptions				
Mean	£46	£83	£76	£67
(SD)	(£68)	(£80)	(£70)	(£75)
Median	£21	£60	£56	£41
Total costs				
Mean	£712	£809	£593	£707
(SD)	(£1381)	(£1650)	(£725)	(£1319)
Median	£284	£418	£359	£356
95% CI ^a	£486 to £1062	£590 to £1431	£459 to £772	£576 to £897

^a Bootstrapped using 5000 replications.

randomised to the TCA arm. The costs of antidepressant prescriptions were lowest for this group, as were costs of non-antidepressant prescriptions. Overall, the mean total cost was highest for patients randomised to SSRIs and lowest for those randomised to LOF, although this was not statistically significant (KW $\chi^2 = 3.76$, $df = 2$, $p = 0.153$). The main items driving costs were inpatient stay (approximately 30% of total costs) followed by GP contacts (approximately 25% of total costs) and drug costs (approximately 22% of total costs). Antidepressant drug costs accounted for less than 10% of total costs.

The costs of this subgroup of patients who completed HADS questionnaires were somewhat different to those estimated for the full 12-month period for the whole cohort reported in the section 'Costs and resource use' (p. 53). When measured for the larger cohort of patients to 12 months, the mean total costs were slightly greater than reported for the cost-effectiveness analyses for the TCA and SSRI groups. However, the mean costs for the LOF group were substantially higher when measured to 12 months (£867) than when estimated for patients included in the cost-effectiveness analysis up to time of last completed HADS questionnaire (£593).

Incremental cost-effectiveness

Table 45 details the results of the incremental cost-effectiveness analysis. On average, patients

randomised to the SSRI group had a greater number of depression-free weeks than either of the other two arms. However, all of the confidence intervals include zero, indicating that there is a possibility that any one treatment strategy could produce more depression-free weeks or involve fewer costs than another. The incremental cost per depression-free week suggests that, assuming those randomised to each class are representative of patients taking that class of antidepressant, the mean additional cost of an extra depression-free week from SSRIs is £59 compared with TCAs and £32 compared with LOF. It was not possible to calculate reliable confidence intervals around mean ratios as the small differences in effect led to unstable ratios. Therefore, cost-effectiveness planes and a CEAC have been used to demonstrate the uncertainty around mean ratios. Figures 10–12 show the cost-effectiveness planes for each comparison.

In Figures 10–12, the difference in depression-free weeks is shown on the horizontal axis and the difference in costs on the vertical axis. Each point on the figure represents a bootstrap replication, where a sample of observations has been drawn from the data, with replacement, and a mean value calculated. Thus, Figure 10 demonstrates that on average the SSRI group received a greater number of depression-free weeks at an additional cost (as the greatest number of mean replications falls in the north-east quadrant) compared with the LOF group. There is, however, an element of

TABLE 45 Incremental analysis of cost-effectiveness

	SSRI vs LOF	TCA vs LOF	SSRI vs TCA
Mean incremental DFWs (95% CI ^a)	3.69 (-1.81 to 9.65)	0.65 (-5.37 to 6.01)	3.04 (-2.10 to 8.81)
Mean incremental costs (95% CI ^a)	£216 (-£47 to £818)	£119 (-£169 to £470)	£97 (-£266 to £658)
Mean incremental cost per DEW ^b	£59	£183	£32

^a Bootstrapped using 5000 replications.
^b Calculated manually as the bootstrap results were unstable owing to small differences in effect.

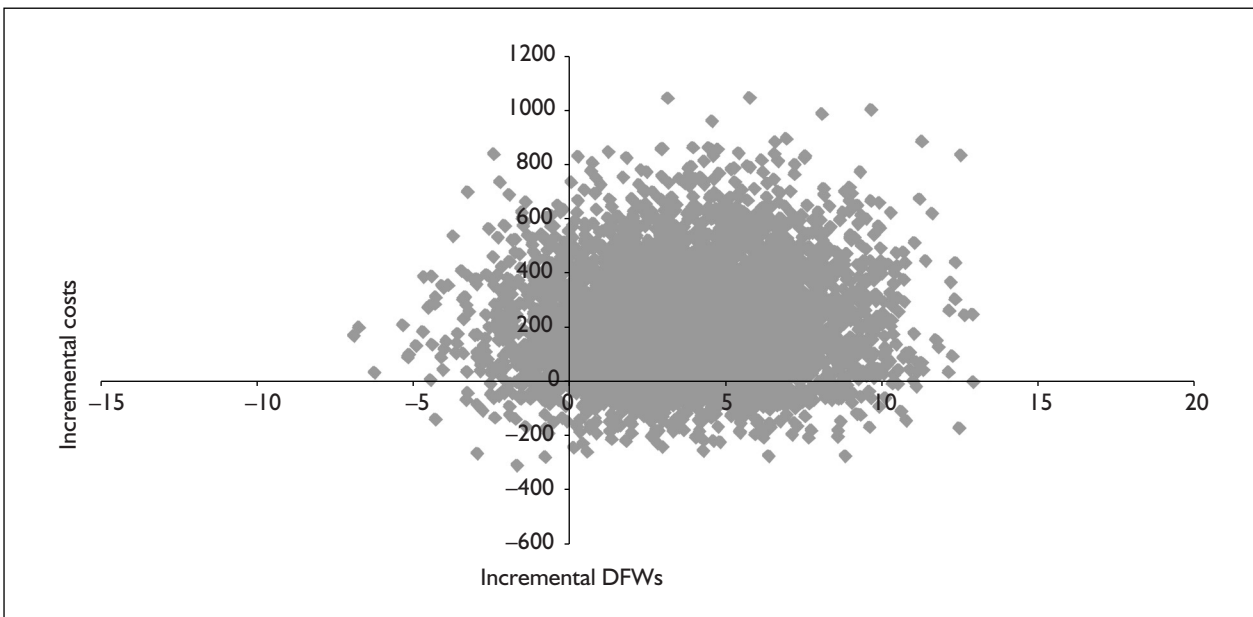


FIGURE 10 Cost-effectiveness plane for the comparison of SSRIs with LOF (using a HADS cut-off of 8)

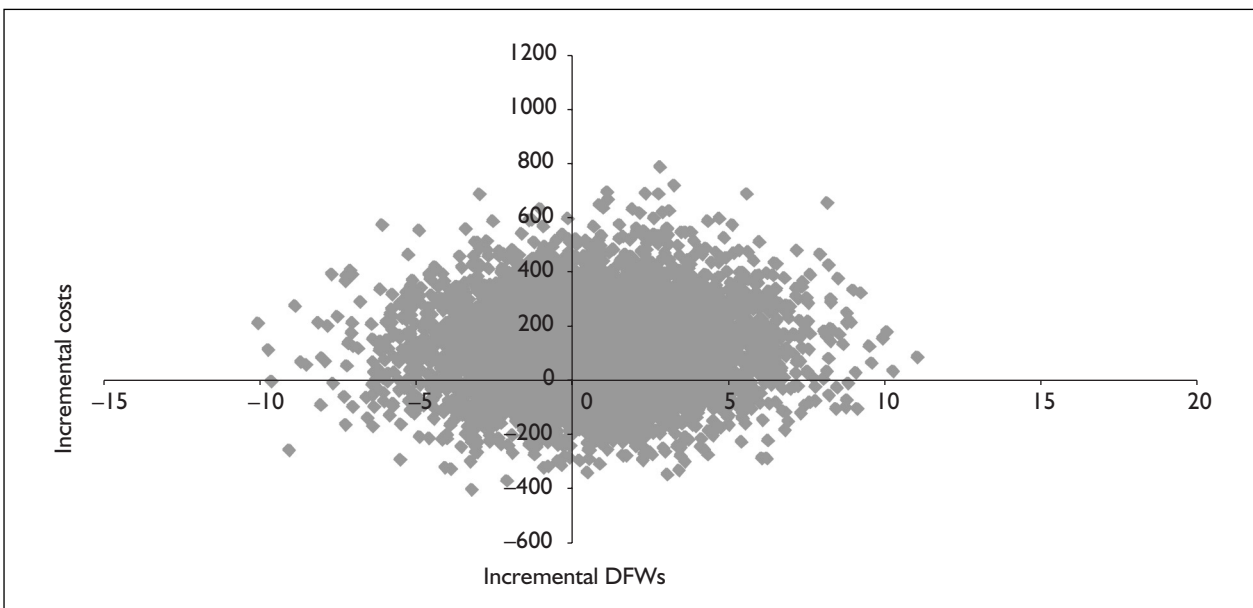


FIGURE 11 Cost-effectiveness plane for the comparison of TCAs with LOF (using a HADS cut-off of 8)

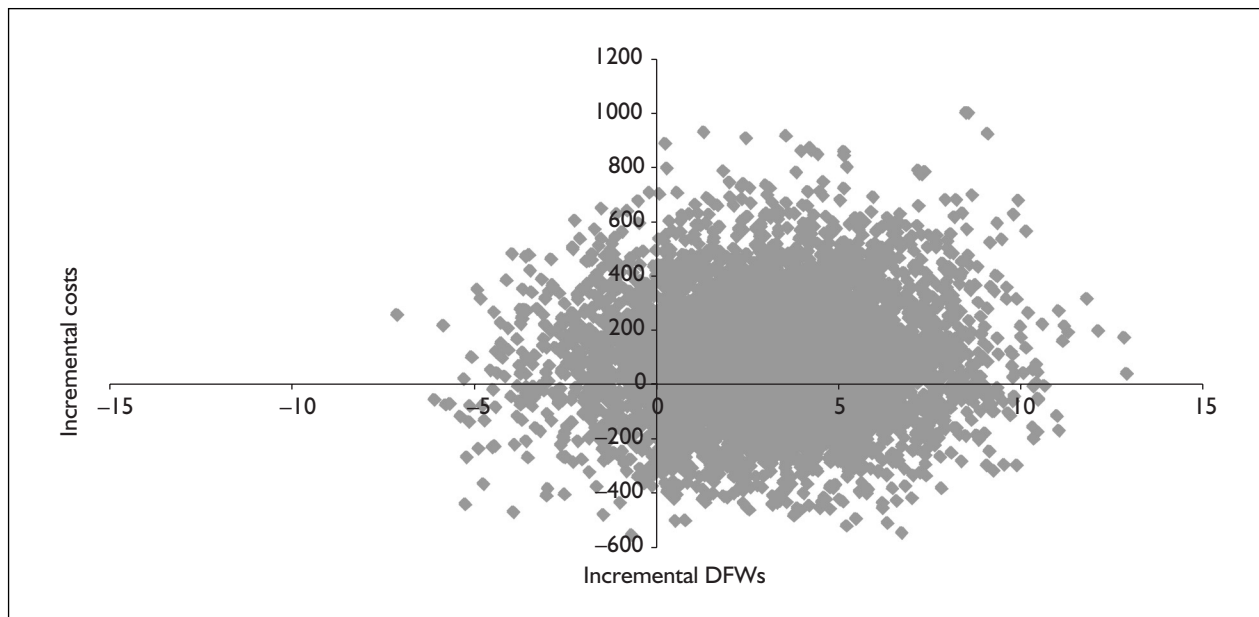


FIGURE 12 Cost-effectiveness plane for the comparison of SSRIs with TCAs (using a HADS cut-off 8)

uncertainty around this conclusion as a small number of observations fall in the other three quadrants of the figure.

Figures 11 and 12 show cost-effectiveness planes for the comparisons of the TCA group with LOF and SSRIs. Figure 11 demonstrates the large amount of uncertainty surrounding the cost-effectiveness of TCAs compared with LOF. The figure shows that although on average the TCA group was more costly than the LOF group there is a large amount of variation in incremental costs, and it appears that there is little difference in effectiveness between the two groups as a similar proportion of replications falls either side of the vertical axis. Figure 12 shows that compared with TCAs, on average the group randomised to SSRIs had a greater number of depression-free weeks at an additional cost. Again, this is subject to a substantial amount of variation, particularly around incremental costs. The uncertainty around these conclusions is quantified in the CEAC shown in Figure 13.

Each point on a line in Figure 13 represents the probability of that treatment being the most cost-effective option for a given value (or 'the most a health system can pay') for an additional depression-free week. For example, if the most a system could afford for an additional depression-free week was £10, prescribing TCAs as the first line treatment would be the cost-effective option approximately 20% of the time, SSRIs 15% of the time and LOF 65% of the time, based on the

results of this analysis. Thus, it appears from these data that, up to a value of just over £50 per depression-free week, a first line treatment of LOF is most likely to be the most cost-effective strategy. Above this value, SSRIs would be the most cost-effective treatment strategy.

Cost-utility analysis

Patient sample

Two-hundred and sixty-two patients reported EQ-5D information at baseline and at least one point during follow-up. The resource-use records for one patient were paper based and not available at the practice, therefore this patient was excluded from the analysis. Thus, the total number of observations in this cost-utility analysis is 261. The lengths of follow-up are presented in Table 46.

Outcomes (QALYs)

EQ-5D tariff scores were used to weight survival and calculate QALYs (Table 47). Two patients died during the study, and these deaths were unrelated to treatment. As with all patients included in the analysis, the QALYs for these patients have been calculated up to the time of their last completed EQ-5D questionnaire.

Summaries of unadjusted EQ-5D values for each group are presented in Appendix 13 (Table 67, Figures 34–37). Small differences in baseline EQ-5D scores were found between the three groups.

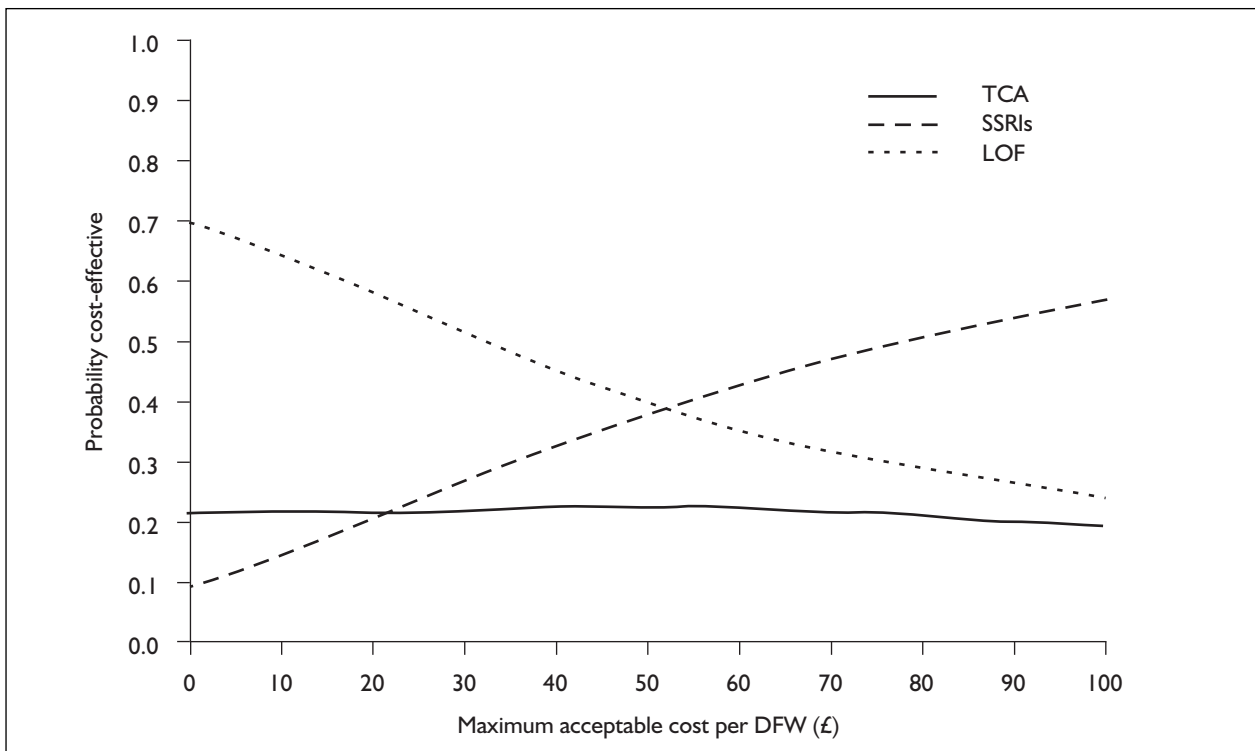


FIGURE 13 CEAC: cost per depression-free week (using a HADS cut-off of 8)

TABLE 46 Summary of length of follow-up from randomisation to date of last EQ-5D (weeks)

	TCA (n = 93)	SSRI (n = 85)	LOF (n = 83)	All (n = 261)
Mean	37	40	38	38
(SD)	(18)	(17)	(17)	(17)
Median	47	48	47	47

TABLE 47 Summary of adjusted reported EQ-5D tariff scores for patients included in the cost-utility analysis

	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
TCA							
n	93	75	58	76	58	53	58
Mean	0.577	0.724	0.771	0.749	0.743	0.777	0.781
(SD)	(0.271)	(0.182)	(0.202)	(0.219)	(0.214)	0.217	(0.189)
SSRI							
n	85	67	57	71	62	56	56
Mean	0.608	0.700	0.752	0.720	0.734	0.785	0.781
(SD)	(0.282)	(0.183)	(0.170)	(0.209)	(0.210)	0.181	(0.185)
LOF							
n	83	59	57	71	52	44	48
Mean	0.574	0.685	0.766	0.746	0.773	0.788	0.767
(SD)	(0.273)	(0.235)	(0.213)	(0.180)	(0.195)	0.176	(0.211)
All patients							
n	261	201	172	218	172	153	162
Mean	0.586	0.705	0.763	0.738	0.749	0.783	0.777
(SD)	(0.275)	(0.199)	(0.195)	(0.203)	(0.207)	0.192	(0.194)

TABLE 48 Summary of adjusted QALYs for patients included in the cost–utility analysis

	TCA (n = 93)	SSRI (n = 85)	LOF (n = 83)	All (n = 261)
Mean	0.548	0.586	0.552	0.562
(SD)	(0.308)	(0.279)	(0.276)	(0.288)
Median	0.669	0.715	0.625	0.667
95% CI ^a	0.481 to 0.606	0.523 to 0.641	0.493 to 0.612	0.525 to 0.594

^a Bootstrapped using 5000 replications.

TABLE 49 Summary of costs from randomisation to date of last EQ-5D

	TCA (n = 93)	SSRI (n = 85)	LOF (n = 83)	All (n = 261)
Non-drug service use				
Mean	£614	£613	£440	£559
(SD)	(£1341)	(£1488)	(£594)	(£1212)
Median	£224	£273	£248	£247
All prescriptions				
Mean	£98	£204	£178	£158
(SD)	(£134)	(£316)	(£255)	(£248)
Median	£53	£110	£88	£78
Of which antidepressant prescriptions				
Mean	£46	£84	£75	£68
(SD)	(£69)	(£81)	(£70)	(£75)
Median	£20	£62	£54	£41
Total costs				
Mean	£712	£817	£619	£717
(SD)	(£1393)	(£1667)	(£757)	(£1331)
Median	£284	£418	£360	£358
95% CI ^a	£502 to £1103	£586 to £1486	£469 to £788	£586 to £924

^a Bootstrapped using 5000 replications.

Mean baseline EQ-5D scores were 0.577 for the TCA group, 0.608 for the SSRI group and 0.574 for the LOF group. Although these differences were not statistically significant, small differences at baseline may lead to biased results.¹¹³ *Table 48* summarises EQ-5D scores after adjusting for this imbalance at baseline, and the distributions of scores are shown in *Figures 38–41* in Appendix 13.

The effect of the adjustment is to decrease the EQ-5D scores for the SSRI group postbaseline, and to increase scores for the LOF group. The effect on the TCA arm is more complicated. The models used to adjust scores were run separately for responses at each time-point. Therefore, they take into account the baseline EQ-5D values of only those patients who responded to the EQ-5D at that specific time-point. When examining the baseline scores of patients who responded at each of the time-points postbaseline separately, the TCA arm had higher baseline EQ-5D scores than

appeared when considering all 261 patients. For example, the baseline scores for the 172 patients who completed the EQ-5D at month 6 were 0.628, 0.613 and 0.569 for the TCA, SSRI and LOF groups, respectively.

Results of QALYs for each of the groups are presented in *Table 48*. The group of patients randomised to SSRIs had the highest mean QALYs over the study period. The QALYs for the TCA and LOF groups were broadly similar, and 95% confidence intervals overlapped for all three groups.

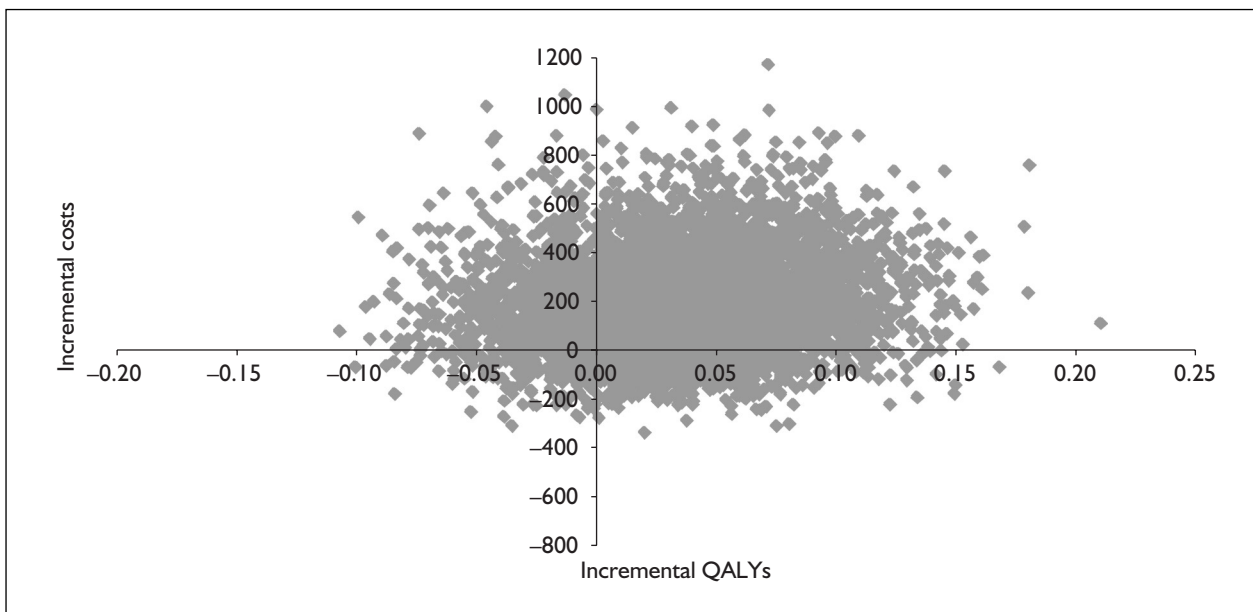
Resource use and costs

The mean levels of resource use measured between randomisation and EQ-5D are presented in Appendix 13 (*Tables 68* and *69*). These can be compared with levels measured up to time of last HADS questionnaire as presented in *Tables 43* and *44*. A summary of the costs of patients included in the cost–utility analysis, measured from time of

TABLE 50 Incremental analysis of cost–utility

	SSRI vs LOF	TCA vs LOF	SSRI vs TCA
Mean incremental QALYs (95% CI ^a)	0.035 (–0.053 to 0.115)	–0.004 (–0.091 to 0.084)	0.039 (–0.046 to 0.123)
Mean incremental costs (95% CI ^a)	£199 (–£68 to £877)	£93 (–£167 to £524)	£105 (–£285 to £637)
Mean incremental cost per QALY ^b	£5686	–£23,250	£2692

^a Bootstrapped using 5000 replications.
^b Calculated manually as the bootstrap results were unstable owing to small differences in effect.

**FIGURE 14** Cost–utility plane for the comparison of SSRIs with LOF

randomisation to the time of their last completed EQ-5D, is shown in *Table 49*. These did not differ greatly from the costs measured to time of last completed HADS, and the greatest difference was an increase of £26 in the mean total cost of those randomised to LOF.

Incremental cost–utility analysis

Table 50 shows the means and 95% confidence intervals of QALYs, costs and incremental cost–utility ratios for each of the three comparisons. The pattern of results is similar to that seen in the cost–effectiveness analysis. The results are again presented graphically in cost–effectiveness planes (*Figures 14–16*). The group randomised to SSRIs had a small QALY gain, at an additional cost, compared with either TCAs or LOF. There was little difference in QALYs between those randomised to TCAs and those randomised to LOF, and the TCA arm had slightly higher

mean costs. The incremental cost per QALY ratios show that the incremental costs of producing an extra QALY from SSRIs as a first line treatment are, on average, £5686 compared with LOF and £2692 compared with TCAs. The uncertainty around the mean results is illustrated in the cost–effectiveness planes by bootstrap replications that span all four quadrants in each comparison.

As it was not possible to calculate confidence intervals, the uncertainty around the mean cost–utility ratios has been incorporated using CEACs (*Figure 17*). The figure demonstrates the chance of each treatment being the most cost-effective strategy for different values placed on an additional QALY. If the value placed on an additional QALY is greater than £5000, then the ITT with SSRIs will be the most cost-effective strategy the majority of the time, based on these data. However, because of the variation within the

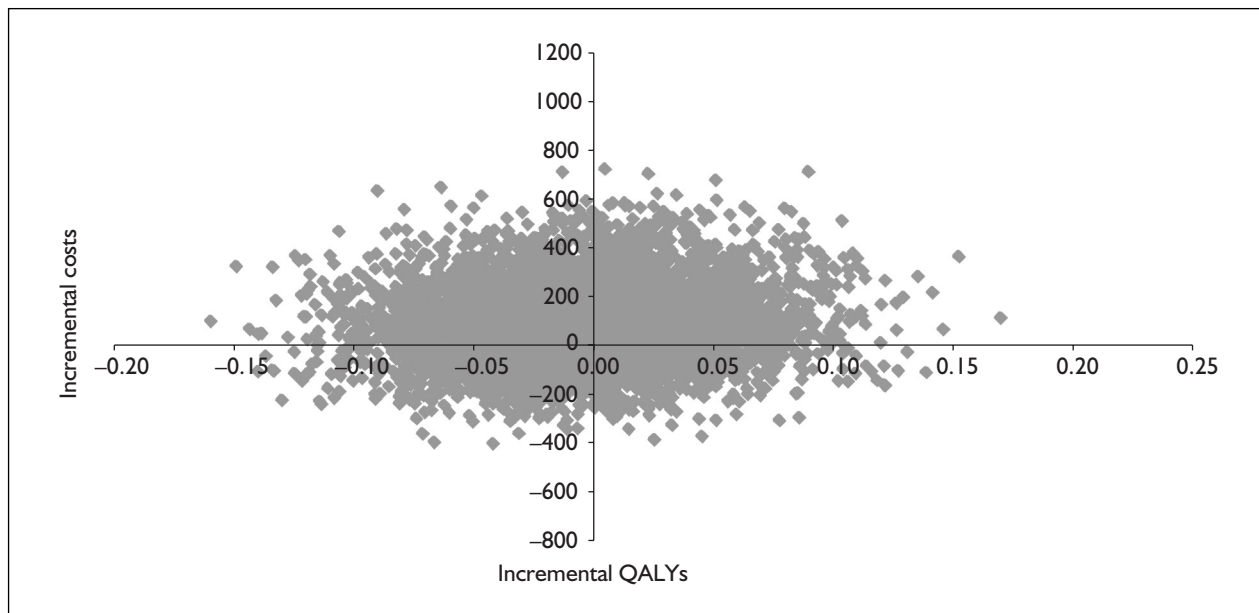


FIGURE 15 Cost-utility plane for the comparison of TCAs with LOF

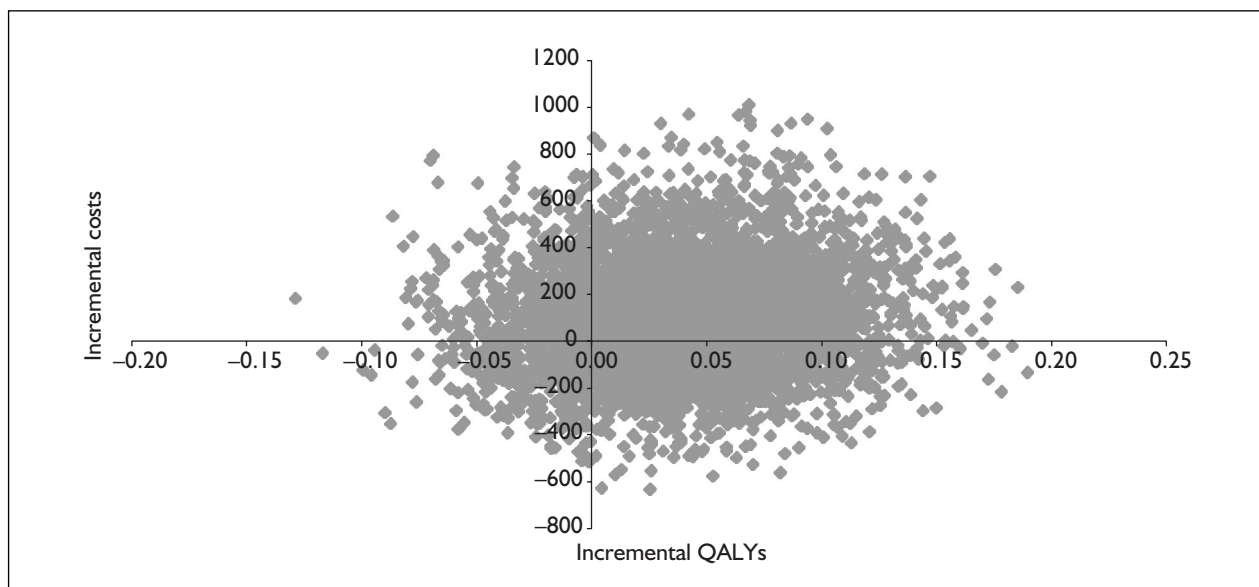


FIGURE 16 Cost-utility plane for the comparison of SSRIs with TCAs

data the probability that the SSRI treatment strategy is the most cost-effective option does not exceed 0.7 for any value placed on a QALY.

Sensitivity analyses

Sensitivity analysis A: using a cut-off of 11 on the HADS to define depression

In the main analysis a cut-off of 8 on the HAD-D scale was used to categorise patients as 'depressed'

or 'depression free'. To test the robustness of the results to this, essentially arbitrary, definition, a cut-off of 11 on the HAD-D scale was instead used to define 'depression free' and the analysis was repeated. The patients included in the analysis and their associated costs were identical to those described in the section 'Cost-effectiveness analysis' (p. 54). *Table 51* provides a summary of depression-free weeks, defined as scoring less than 11 on the HADS questionnaire. As expected, the number of depression-free weeks increased when

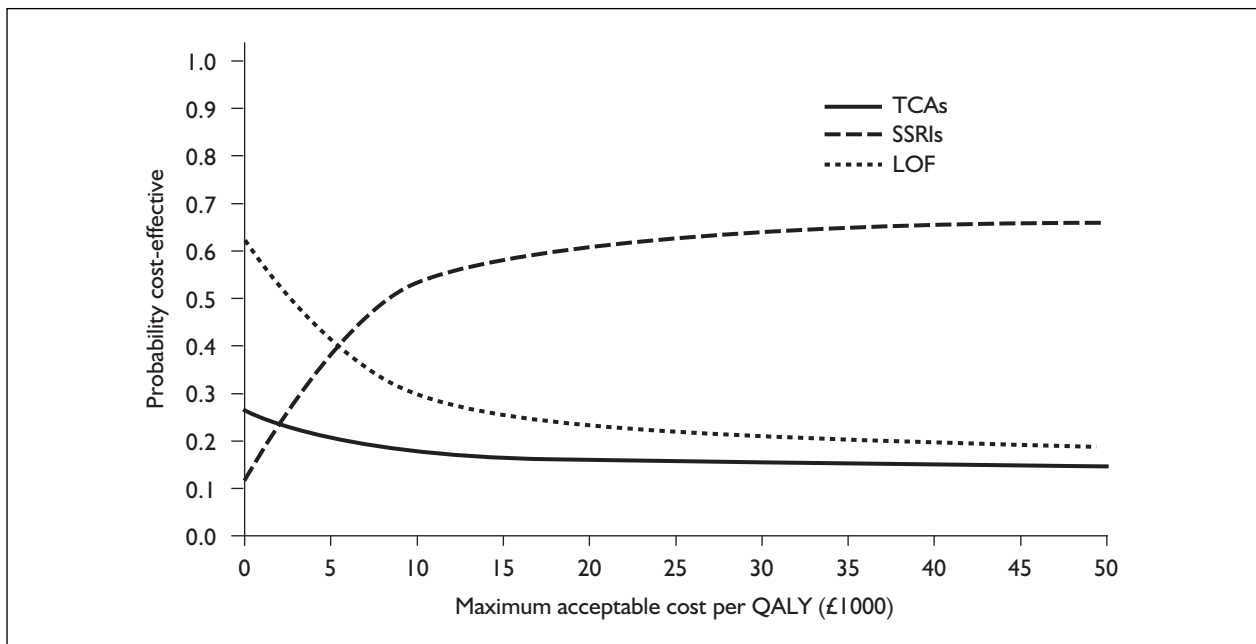


FIGURE 17 CEAC: cost per QALY

TABLE 51 Summary of depression-free weeks to date of last HADS (using a cut-off of 11)

	TCA (n = 95)	SSRI (n = 87)	LOF (n = 82)	All (n = 264)
Mean	33.21	35.10	32.00	33.47
(SD)	(18.24)	(17.93)	(18.30)	(18.15)
Median	43.64	43.48	36.60	42.84
95% CI ^a	29.2 to 36.6	31.0 to 38.5	28.0 to 36.1	31.1 to 35.5

^a Bootstrapped using 5000 replications.

TABLE 52 Incremental analysis of cost-effectiveness (using a HADS cut-off of 11)

	SSRI vs LOF	TCA vs LOF	SSRI vs TCA
Mean incremental DFWs (95% CI ^a)	3.10 (-2.34 to 8.38)	1.22 (-4.37 to 6.40)	1.87 (-3.21 to 7.36)
Mean incremental costs (95% CI ^a)	£216 (-£47 to £818)	£119 (-£169 to £470)	£97 (-£266 to £658)
Mean incremental cost per DFW ^b	£70	£98	£52

^a Bootstrapped using 5000 replications.
^b Calculated manually as the bootstrap results were unstable owing to small differences in effect.

the looser definition of depression free is applied (overall mean with cut-off of 8 was 26.05 compared with 33.47 with a cut-off of 11). The general pattern of the means remained the same as that when a cut-off of 8 was used (SSRI had the largest mean, followed by TCAs, then LOF).

The incremental analysis shown in Table 52 shows that there is still a gain in depression-free weeks for the SSRI group, but that this gain has

diminished relative to the analysis using a cut-off of 8. It also appears that TCAs compare more favourably with both SSRIs and LOF than in the main analysis. Thus, whereas the mean ICER for SSRIs compared with the LOF strategy remains relatively stable (£70 compared with £59), using a cut-off of 8 on the HADS makes the TCA strategy appear slightly less cost-effective than when a cut-off of 11 is used to define depression (see Table 45).

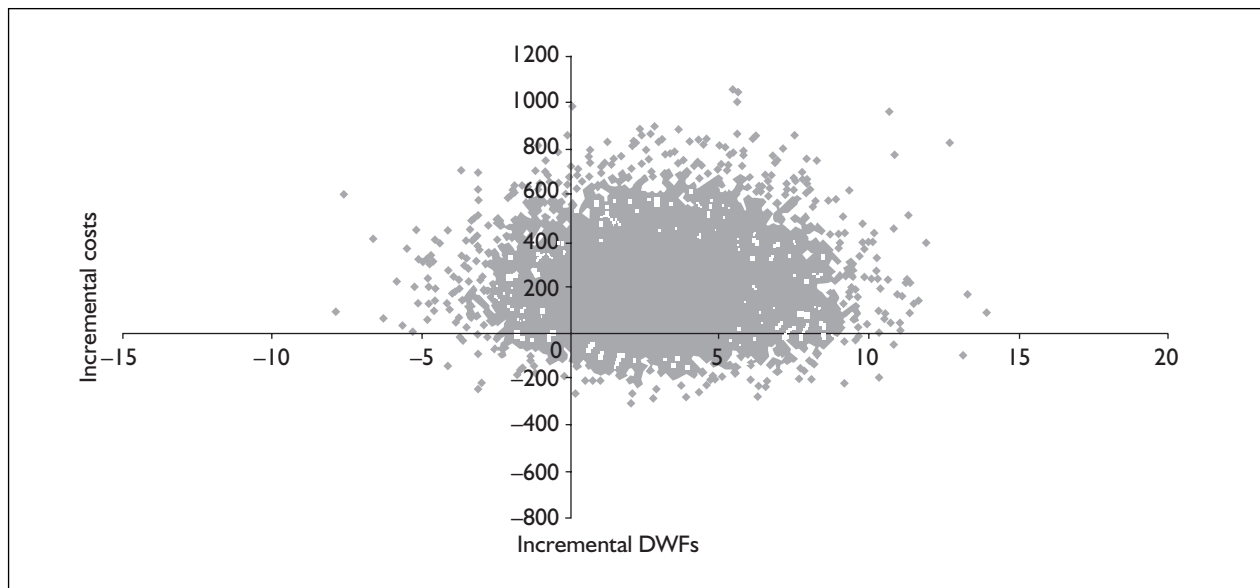


FIGURE 18 Cost-effectiveness plane for the comparison of SSRIs with LOF (using a HADS cut-off of 11)

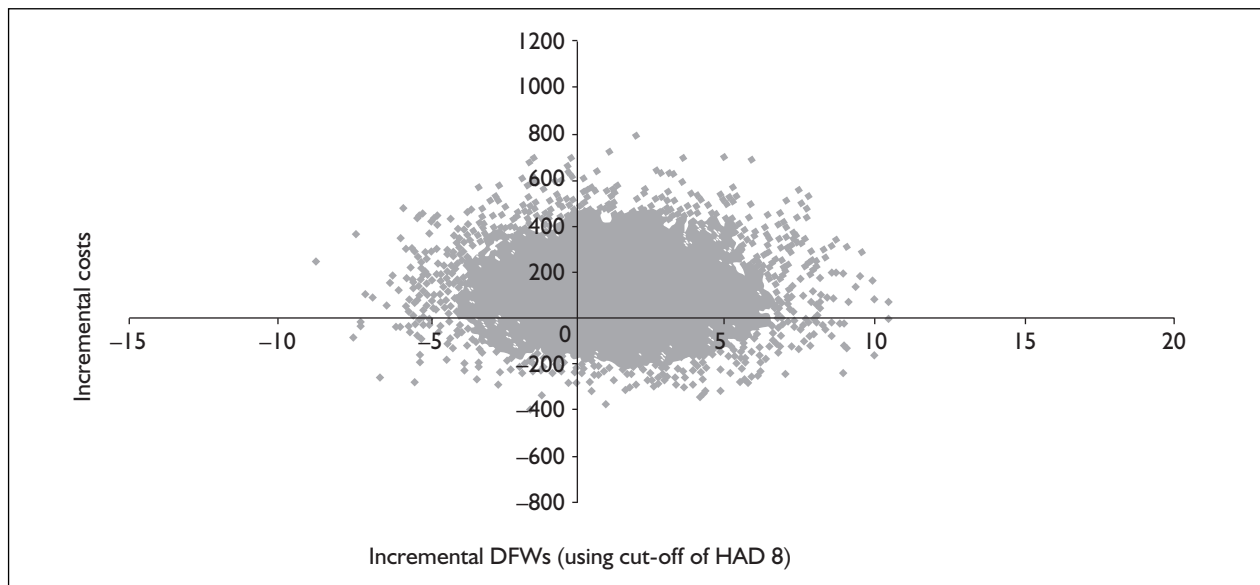


FIGURE 19 Cost-effectiveness plane for the comparison of TCAs with LOF (using a HADS cut-off of 11)

Figures 18–20 show that the cost-effectiveness planes using a cut-off of 11 on the HADS to define a depression-free week are similar to those presented for the analysis using a cut-off of 8. The CEAC in Figure 21 shows a similar pattern to the curve in the main analysis (Figure 13). However, the intersection between the curves for the SSRI and LOF strategy has shifted to the right, indicating that the maximum acceptable cost per depression-free week must be approximately £60 or greater for the SSRI treatment strategy to be, on average, the most cost-effective strategy.

Sensitivity analysis B: including only patients who accepted their randomised treatment

The results from the main analyses demonstrated that the same conclusions were drawn when expressing cost-effectiveness in terms of a depression-free week or in terms of a QALY, and as cost per QALY ratios are the more commonly used, the remaining sensitivity analyses were performed using only the latter outcome measure. This analysis included only those patients who initially accepted their randomised treatment,

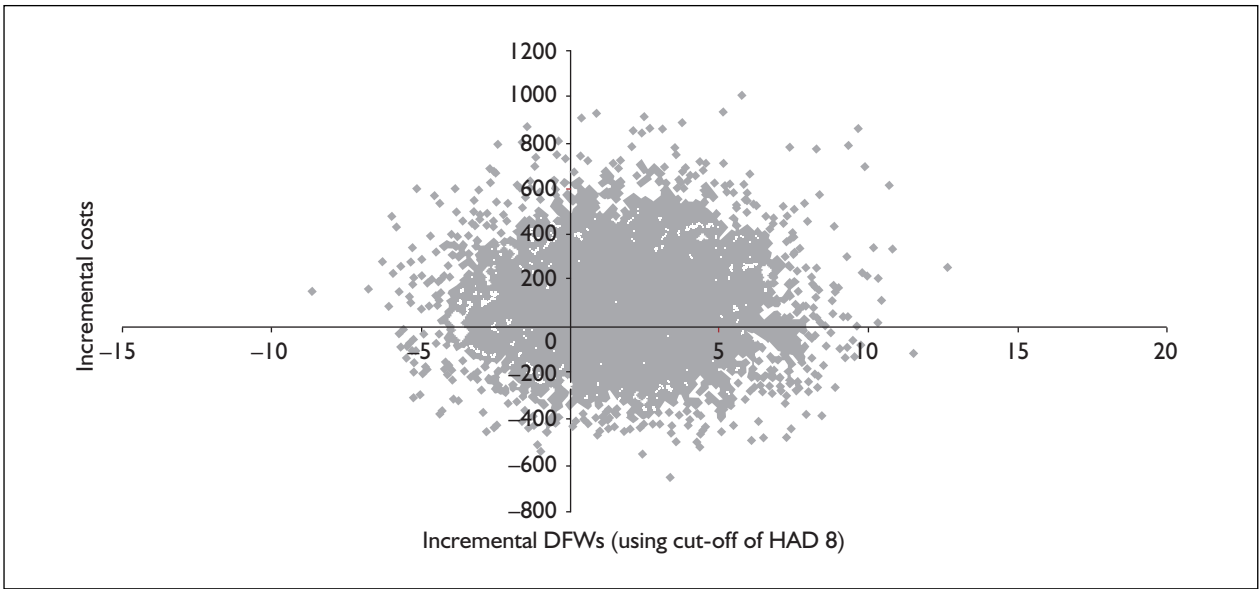


FIGURE 20 Cost-effectiveness plane for the comparison of SSRIs with TCAs (using a HADS cut-off of 11)

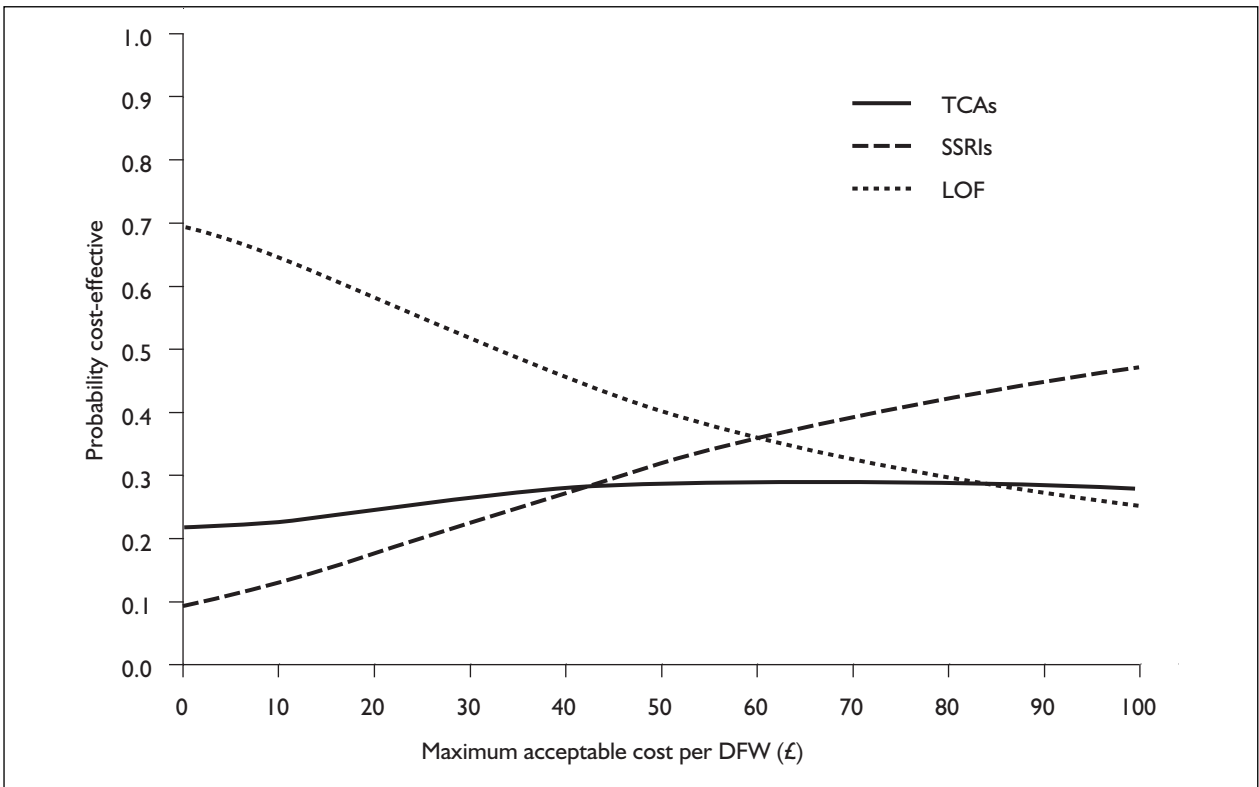


FIGURE 21 CEAC (using a HADS cut-off of 11)

regardless of whether they later switched to an alternative treatment. The methods used in the analysis were identical to those used in the section ‘Cost-utility analysis’ (p. 58).

Two-hundred and thirty-five patients accepted their randomised treatment. Of these, 193

patients reported EQ-5D information at baseline and at least one point postbaseline. The resource-use records for one patient were paper based and not available at the practice, therefore this patient was excluded from this economic analysis. Thus, the total number of observations in this cost-effectiveness analysis is 192. The mean lengths of

TABLE 53 Summary of length of follow-up from randomisation to date of last EQ-5D (weeks) (acceptors only)

	TCA (n = 56)	SSRI (n = 74)	LOF (n = 62)	All (n = 192)
Mean	37	39	37	38
(SD)	(18)	(17)	(17)	(18)
Median	47	48	47	47

TABLE 54 Summary of adjusted QALYs for patients included in the cost–utility analysis (acceptors only)

	TCA (n = 56)	SSRI (n = 74)	LOF (n = 62)	All (n = 192)
Mean	0.562	0.575	0.531	0.557
(SD)	(0.308)	(0.286)	(0.279)	(0.289)
Median	0.684	0.702	0.620	0.664
95% CI ^a	0.474 to 0.638	0.510 to 0.640	0.460 to 0.598	0.516 to 0.600

^a Bootstrapped using 5000 replications.

follow-up for patients were similar for the main cost–utility analysis and are presented in *Table 53*.

Table 54 shows the QALY results for patients who accepted their allocated treatment. Overall, there was little difference in the number of QALYs between those who were randomised in the trial (mean = 0.562) and those who accepted their allocated treatment (mean = 0.557). Examination of the data by group showed a small decrease in the mean number of QALYs for the SSRI and LOF groups, and a small increase in the mean number of QALYs for the TCA group.

Details of the costs of the restricted patient sample are shown in *Table 55*. Overall, there was little difference in total costs: £700 in the restricted sample and £717 in the main analysis. The mean costs of all three groups were slightly lower in this sensitivity analysis, and the greatest change was in the LOF group, whose mean cost was £47 less in this sensitivity analysis.

The effect of excluding patients who did not accept their randomised treatment was negligible for the comparison of the SSRI treatment strategy with the LOF strategy (*Table 56*). However, the small change in QALYs for the TCA group has altered the cost-effectiveness ratios such that it now appears that the cost of an extra QALY gained from a switch from the LOF to TCA strategy would be on average £4355, and £7385 from a switch from TCAs to SSRIs. The variation around these mean estimates has also increased (*Figures 22–24*).

As in the previous analyses, it was not possible to calculate reliable confidence intervals around these mean estimates, and this has been incorporated using a CEAC (*Figure 25*). When considering patients who accepted their randomised allocation only, the TCA strategy is more likely to be the most cost-effective strategy compared with LOF, for all values placed on an additional QALY over £5000. The SSRI strategy is still the most likely to be the most cost-effective choice for all values of an additional QALY over £10,000, although there is more uncertainty around this conclusion.

Sensitivity analysis C: cost–utility analysis excluding patients with extreme cost values

Examination of the cost data found that, as is usual with this kind of data, the distribution of costs was heavily positively skewed. The majority of observations were clustered, with the exception of three patients whose costs stood out as extreme outliers relative to the others. This analysis excludes data from these three outlying observations, as these patients may not be typical of the ‘average’ patient. However, it should be borne in mind that in any sample, as in real life, there are likely to be patients with outlying values. Values from all observations, including outliers, should be considered when making inferences from the costs and effects of sampled data about the costs and effects of a population. It is also important to consider the costs of the patients of the total sample in order to relate average costs to total costs. The numbers of patients in each group

TABLE 55 Summary of costs from randomisation to date of last EQ-5D (acceptors only)

	TCA (n = 56)	SSRI (n = 74)	LOF (n = 62)	All (n = 192)
Non-drug service use				
Mean	£621	£606	£419	£550
(SD)	(£1428)	(£1579)	(£591)	(£1288)
Median	£210	£269	£221	£229
All prescriptions				
Mean	£86	£196	£153	£150
(SD)	(£109)	(£330)	(£194)	(£243)
Median	£44	£96	£86	£77
Of which antidepressant prescriptions				
Mean	£44	£97	£78	£75
(SD)	(£62)	(£91)	(£66)	(£78)
Median	£24	£68	£68	£50
Total costs				
Mean	£707	£803	£572	£700
(SD)	(£1446)	(£1765)	(£724)	(£1403)
Median	£259	£414	£316	£335
95% CI ^a	£459 to £1343	£548 to £1584	£431 to £811	£558 to £1008

^a Bootstrapped using 5000 replications.

TABLE 56 Incremental analysis of cost–utility (acceptors only)

	SSRI vs LOF	TCA vs LOF	SSRI vs TCA
Mean incremental QALYs (95% CI ^a)	0.044 (–0.055 to 0.137)	0.031 (–0.084 to 0.134)	0.013 (–0.087 to 0.124)
Mean incremental costs (95% CI ^a)	£231 (–£80 to £929)	£135 (–£182 to £652)	£96 (–£407 to £709)
Mean incremental cost per QALY ^b	£5250	£4355	£7385

^a Bootstrapped using 5000 replications.
^b Calculated manually as the bootstrap results were unstable owing to small differences in effect.

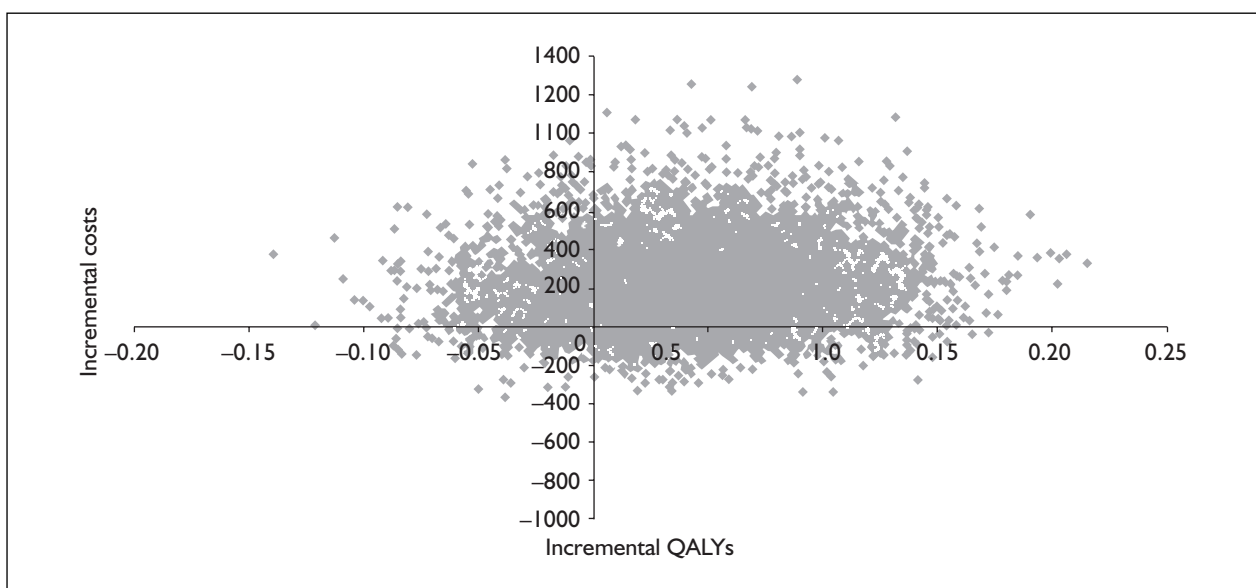


FIGURE 22 Sensitivity analysis: cost–utility plane for the comparison of SSRIs with LOF (acceptors only)

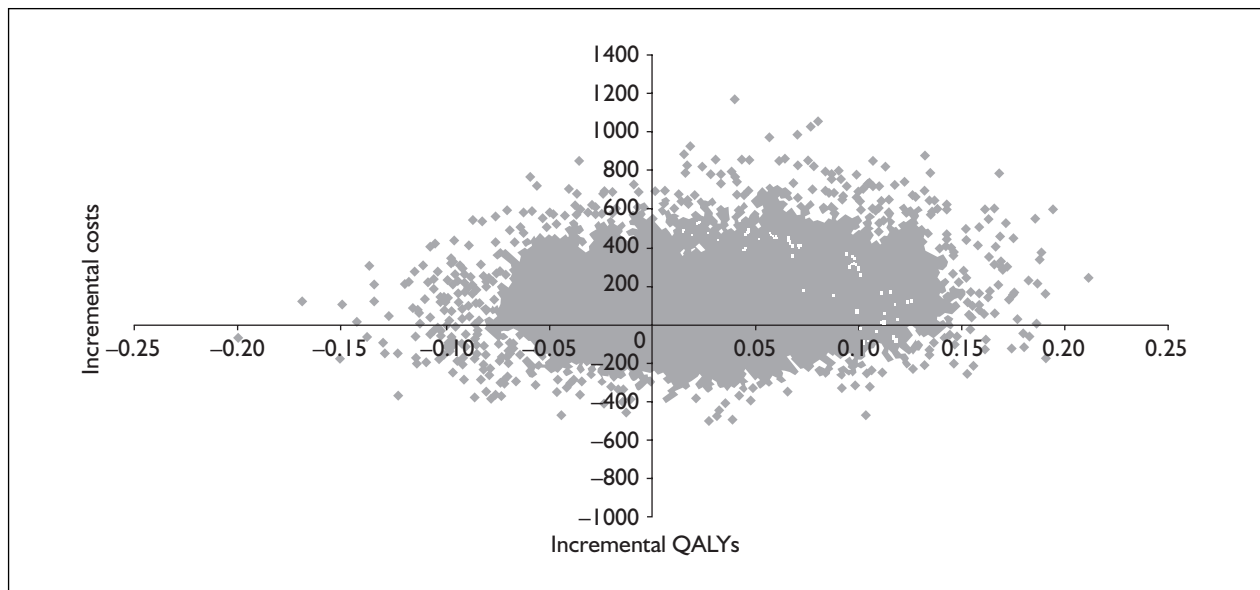


FIGURE 23 Sensitivity analysis: cost–utility plane for the comparison of TCAs with LOF (acceptors only)

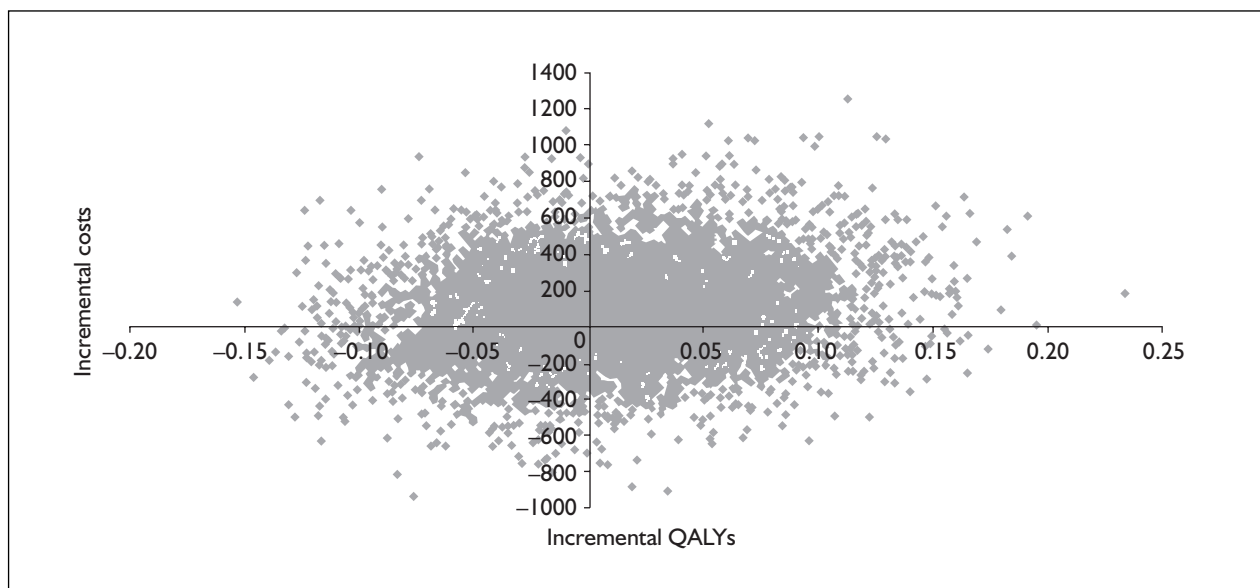


FIGURE 24 Sensitivity analysis: cost–utility plane for the comparison of SSRIs with TCAs (acceptors only)

and a summary of their lengths of follow-up are shown in *Table 57*.

The effects of excluding the three patients from the analysis on the mean QALY values were small. The mean QALYs for the TCA arm decreased slightly, by 0.004, and by 0.001 for the SSRI arm (*Table 58*).

All three excluded patients had some inpatient stay, but also incurred large costs across a range of resource-use items. The effect on costs of excluding the three patients was much more

striking. The mean costs relating to non-drug service use decreased substantially for both the TCA and SSRI groups, resulting in the means of these costs becoming similar across all three groups. The mean total cost of the TCA group was the lowest of the three after the outlier values had been excluded, and the mean total costs of all three groups were more aligned than previously. Also, not surprisingly, the variation in the cost data decreased substantially (*Table 59*).

Excluding the three patients with outlying cost values made little difference to the incremental

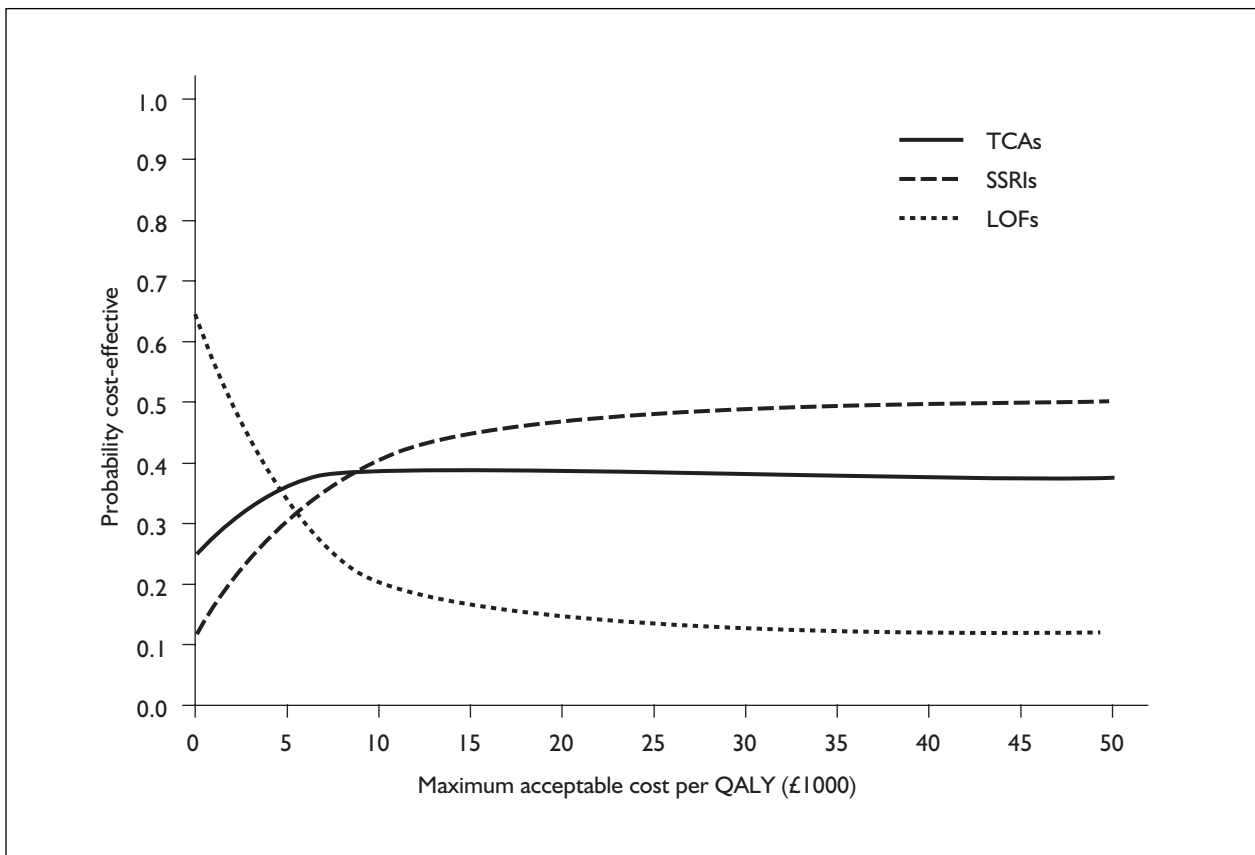


FIGURE 25 CEAC: cost per QALY (acceptors only)

TABLE 57 Summary of length of follow-up from randomisation to date of last EQ-5D (weeks), excluding the values of three patients with outlying cost values

	TCA (n = 93)	SSRI (n = 84)	LOF (n = 83)	All (n = 258)
Mean	36	39	38	38
(SD)	(18)	(17)	(17)	(17)
Median	47	48	47	47

TABLE 58 Summary of adjusted QALYs for patients included in the cost-utility analysis, excluding the values of three patients with outlying cost values

	TCA (n = 91)	SSRI (n = 84)	LOF (n = 83)	All (n = 258)
Mean	0.544	0.585	0.552	0.560
(SD)	(0.311)	(0.280)	(0.276)	(0.289)
Median	0.669	0.715	0.625	0.665
95% CI ^a	0.479 to 0.609	0.522 to 0.644	0.493 to 0.612	0.524 to 0.595

^a Bootstrapped using 5000 replications.

TABLE 59 Summary of costs from randomisation to date of last EQ-5D, excluding the values of three patients with outlying cost values

	TCA (n = 91)	SSRI (n = 84)	LOF (n = 83)	All (n = 258)
Non-drug service use				
Mean	£464	£447	£440	£457
(SD)	(£864)	(£628)	(£594)	(£708)
Median	£217	£271	£248	£236
All prescriptions				
Mean	£96	£189	£178	£153
(SD)	(£135)	(£288)	(£255)	(£236)
Median	£51	£108	£88	£75
Of which antidepressant prescriptions				
Mean	£55	£98	£75	£83
(SD)	(£72)	(£87)	(£70)	(£79)
Median	£29	£75	£54	£57
Total costs				
Mean	£560	£656	£619	£610
(SD)	(£934)	(£759)	(£757)	(£822)
Median	£272	£418	£360	£354
95% CI ^a	£412 to £807	£517 to £854	£469 to £788	£523 to £727

^a Bootstrapped using 5000 replications.

TABLE 60 Incremental analysis of cost–utility, excluding the values of three patients with outlying cost values

	SSRI vs LOF	TCA vs LOF	SSRI vs TCA
Mean incremental QALYs (95% CI ^a)	0.032 (–0.054 to 0.117)	–0.007 (–0.088 to 0.082)	0.040 (–0.050 to 0.127)
Mean incremental costs (95% CI ^a)	£37 (–£203 to £263)	–£58 (–£319 to £196)	£96 (–£171 to £334)
Mean incremental cost per QALY ^b	£1156	£8286	£2400

^a Bootstrapped using 5000 replications.
^b Calculated manually as the bootstrap results were unstable owing to small differences in effect.

QALY values (Table 60). The incremental cost estimates were substantially reduced for both SSRIs and TCAs compared with LOF. The additional cost per QALY gained from SSRIs compared with LOF was just over £1000 after excluding these patients. The additional cost per QALY gained from TCAs compared with LOF was just over £8000. This latter ratio is best considered alongside the cost-effectiveness plane (see Figure 27) as it results from negative incremental costs and negative incremental QALYs.

The cost-effectiveness planes demonstrate the reduced variation in the incremental cost estimates (Figures 26–28). However, there remains a considerable amount of variation in the estimates of QALYs gained.

The CEAC in Figure 29 shows that excluding the three patients with outlying cost values from the

analysis did not greatly affect the conclusions drawn. The SSRI strategy is still likely to be the most cost-effective strategy if the value placed on an additional QALY is greater than £5000. In the main analysis, although it appeared that the probability of LOF being the more cost-effective treatment was greater than for TCA, there was little difference in the probabilities for the LOF and TCA groups. After excluding the three patients, although the TCA strategy now had a slightly greater probability, there was still little difference in the probabilities for these two treatment strategies.

Sensitivity analysis D: cost–utility analysis using March 2003 prices for antidepressant medications

In the main analysis, the unit costs of all drugs were taken from the September 2001 BNF.¹⁰⁷ As the costs of antidepressants have altered since then, especially for the SSRI class, the analysis was

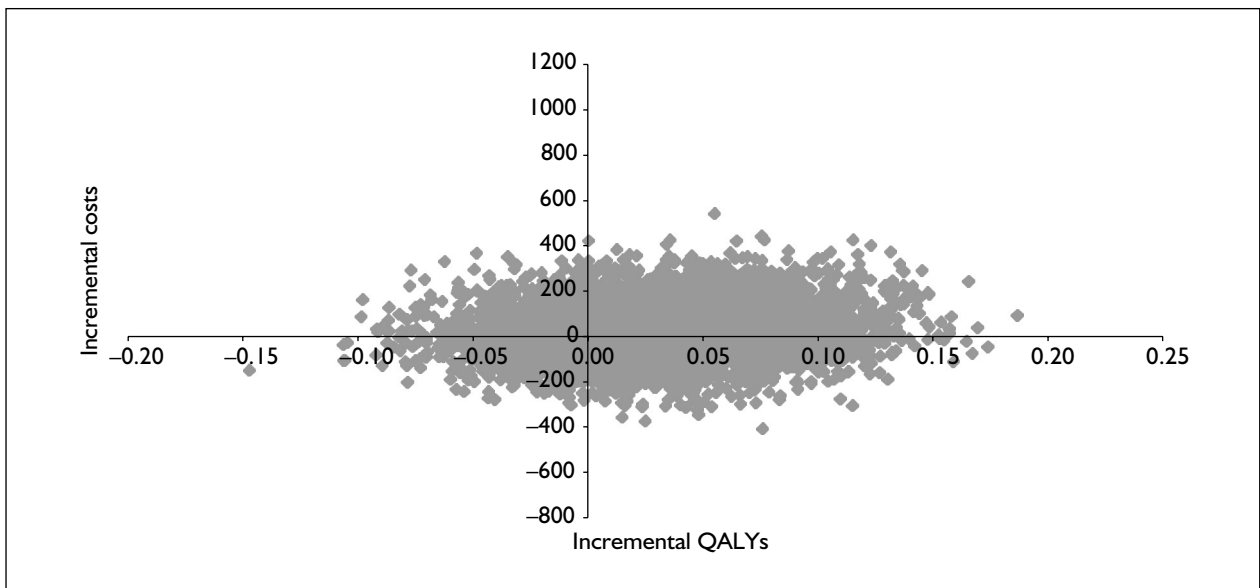


FIGURE 26 Cost-utility plane for the comparison of SSRIs with LOF, excluding the values of three patients with outlying cost values

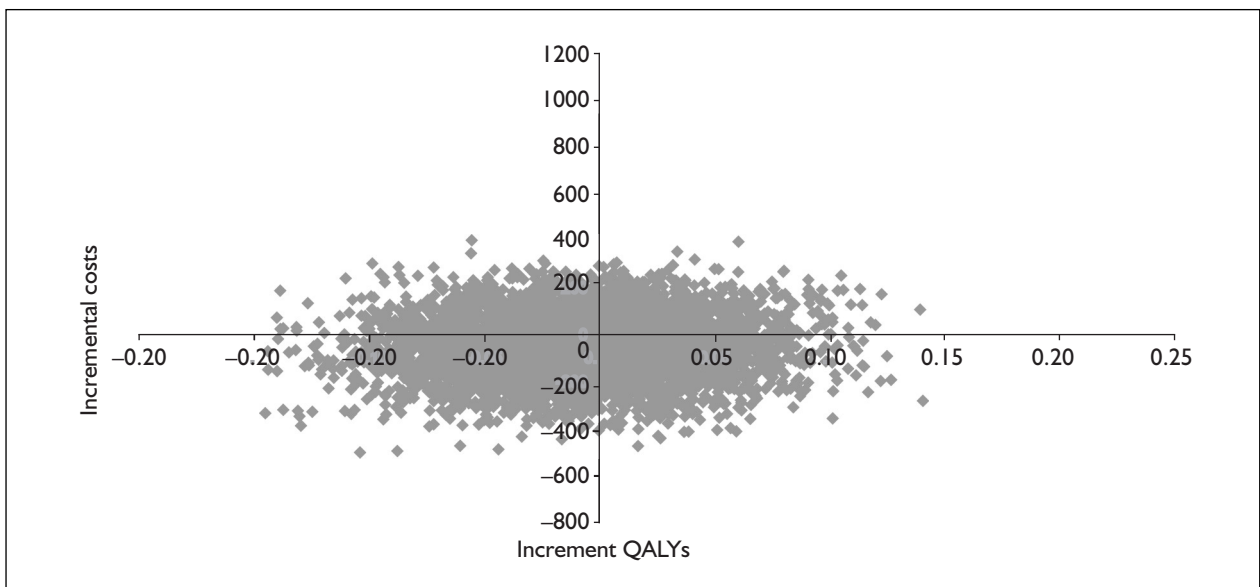


FIGURE 27 Cost-utility plane for the comparison of TCAs with LOF, excluding the values of three patients with outlying cost values

repeated using unit costs for antidepressant medications taken from the March 2003 edition.¹¹⁴ The number of patients included in the analysis and their associated QALYs were identical to those described in the main cost-utility results.

Table 61 shows a summary of the costs estimated using March 2003 prices for antidepressant medications. Overall, there was a decrease in

antidepressant medication costs, although this change was very small and the largest change in mean costs was a reduction of £6 per patient for the SSRI group. The effect of using March 2003 antidepressant prices on the incremental cost-utility analysis was negligible (Table 62, Figures 30–32). There was very little difference between the CEAC in the main analysis and that presented for this sensitivity analysis (Figure 33).

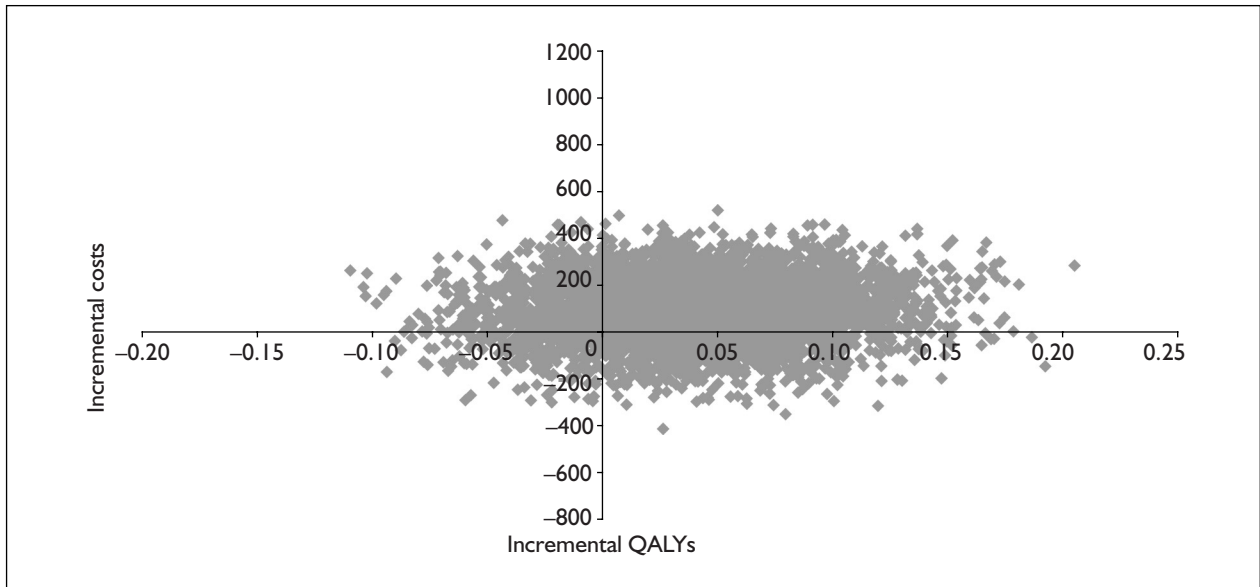


FIGURE 28 Cost–utility plane for the comparison of SSRIs with TCAs, excluding the values of three patients with outlying cost values

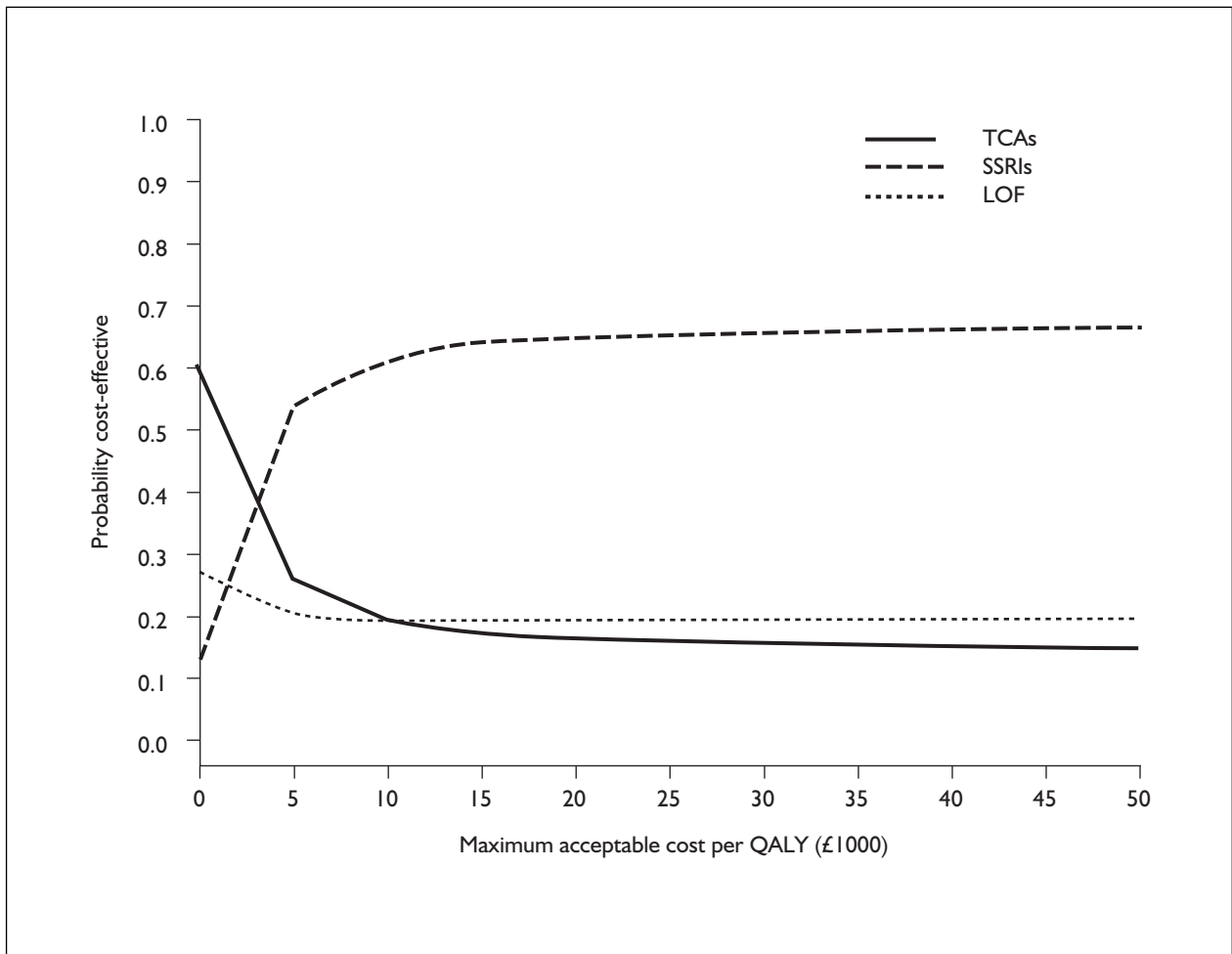


FIGURE 29 CEAC: cost per QALY, excluding the values of three patients with outlying cost values

TABLE 61 Summary of costs from randomisation to date of last EQ-5D (March 2003)

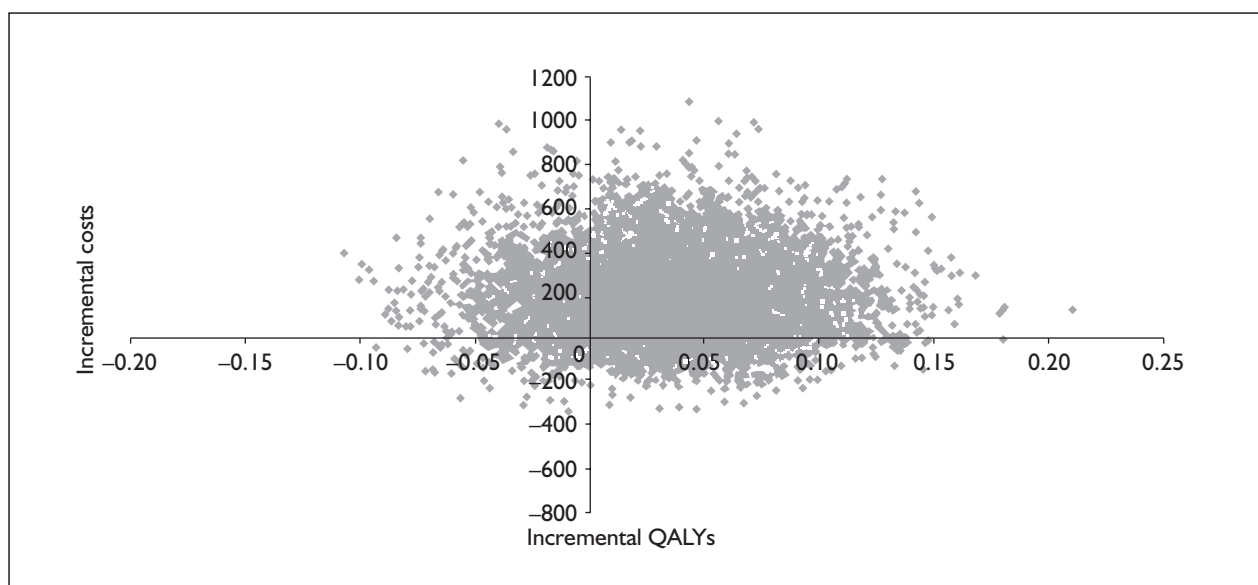
	TCA (n = 93)	SSRI (n = 85)	LOF (n = 83)	All (n = 261)
Non-drug service use				
Mean	£614	£613	£440	£559
(SD)	(£1341)	(£1488)	(£594)	(£1212)
Median	£224	£273	£248	£247
All prescriptions				
Mean	£98	£202	£176	£156
(SD)	(£140)	(£320)	(£255)	(£250)
Median	£51	£110	£82	£78
Of which antidepressant prescriptions				
Mean	£44	£78	£73	£64
(SD)	(£65)	(£76)	(£67)	(£71)
Median	£18	£58	£51	£41
Total costs				
Mean	£711	£816	£616	£715
(SD)	(£1396)	(£1667)	(£756)	(£1332)
Median	£284	£411	£359	£354
95% CI ^a	£492 to £1087	£586 to £1481	£472 to £803	£583 to £912

^a Bootstrapped using 5000 replications.

TABLE 62 Incremental analysis of cost–utility (March 2003)

	SSRI vs LOF	TCA vs LOF	SSRI vs TCA
Mean incremental QALYs (95% CI ^a)	0.035 (–0.053 to 0.115)	–0.004 (–0.091 to 0.084)	0.039 (–0.046 to 0.123)
Mean incremental costs (95% CI ^a)	£199 (–£75 to £847)	£95 (–£179 to £499)	£104 (–£290 to £662)
Mean incremental cost per QALY ^b	£5686	–£23250	£2692

^a Bootstrapped using 5000 replications.
^b Calculated manually as the bootstrap results were unstable owing to small differences in effect.

**FIGURE 30** Cost–utility plane for the comparison of SSRIs with LOF, using March 2003 prices to cost antidepressant drugs

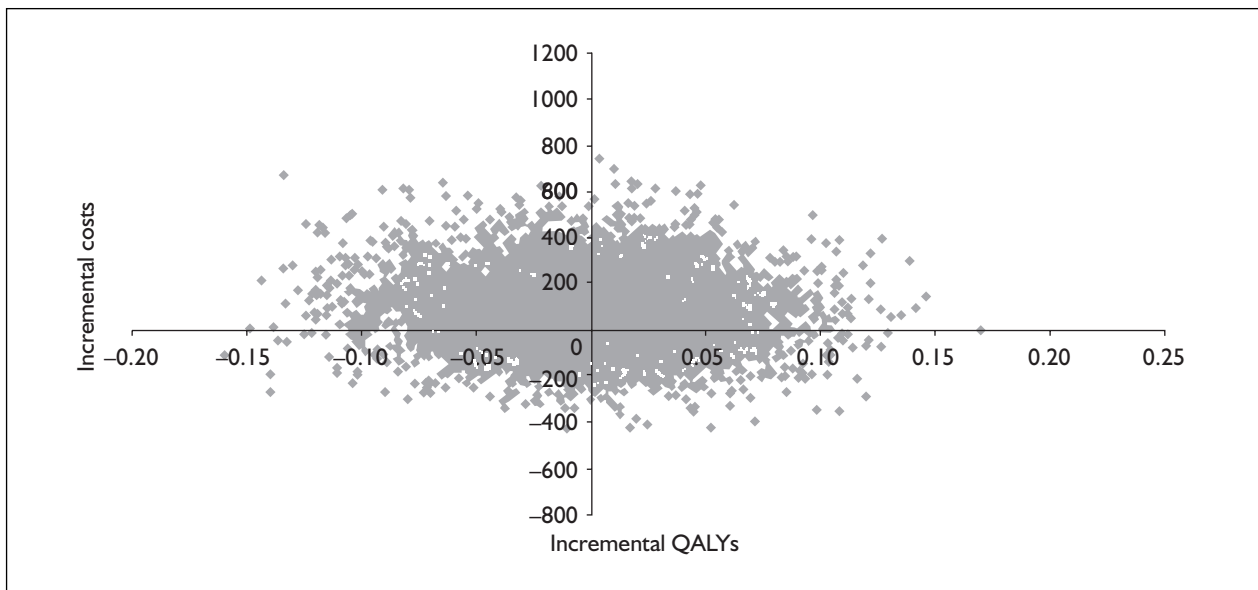


FIGURE 31 Cost–utility plane for the comparison of TCAs with LOF, using March 2003 prices to cost antidepressant drugs

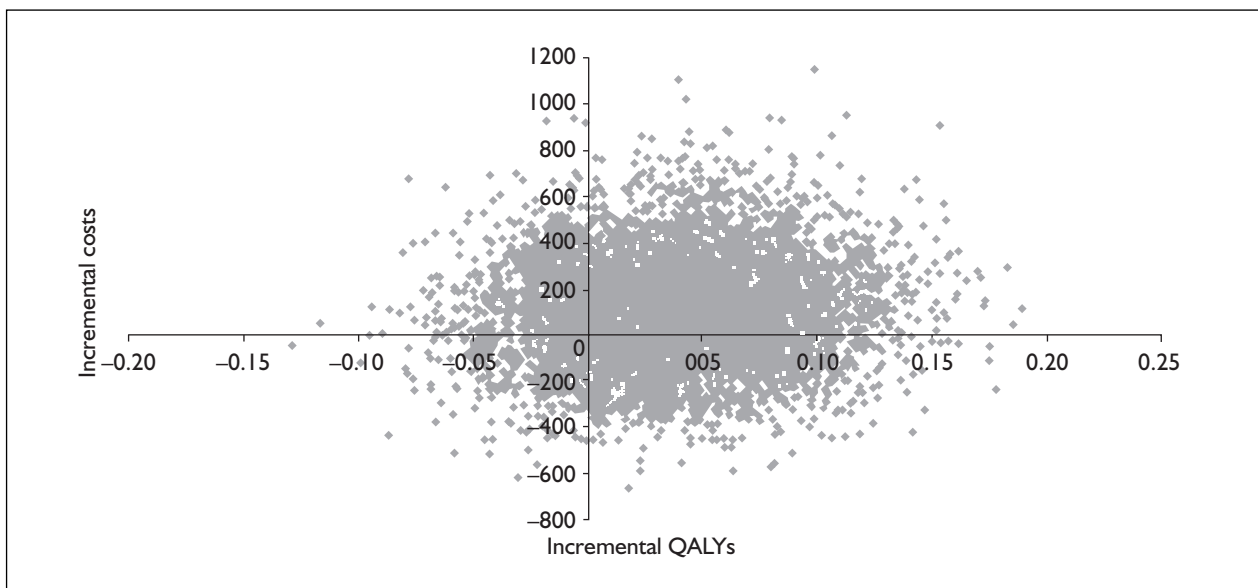


FIGURE 32 Cost–utility plane for the comparison of SSRIs with TCAs, using March 2003 prices to cost antidepressant drugs

Incremental cost–utility analysis

Sensitivity analysis E: summary of costs to 12 months from randomisation of patients with baseline CIS-R diagnosis of depression

As a further check on the generalisability of the results, the total costs to 12 months were compared between treatments in the subsample of

236 patients who met the CIS-R criteria for depressive disorder or mixed anxiety and depression. *Table 63* shows that no differences were observed in total costs. Although this subgroup analysis has even less power than the main analysis, there is no suggestion of enhanced differential cost-effectiveness for any treatment in this more severely affected subgroup.

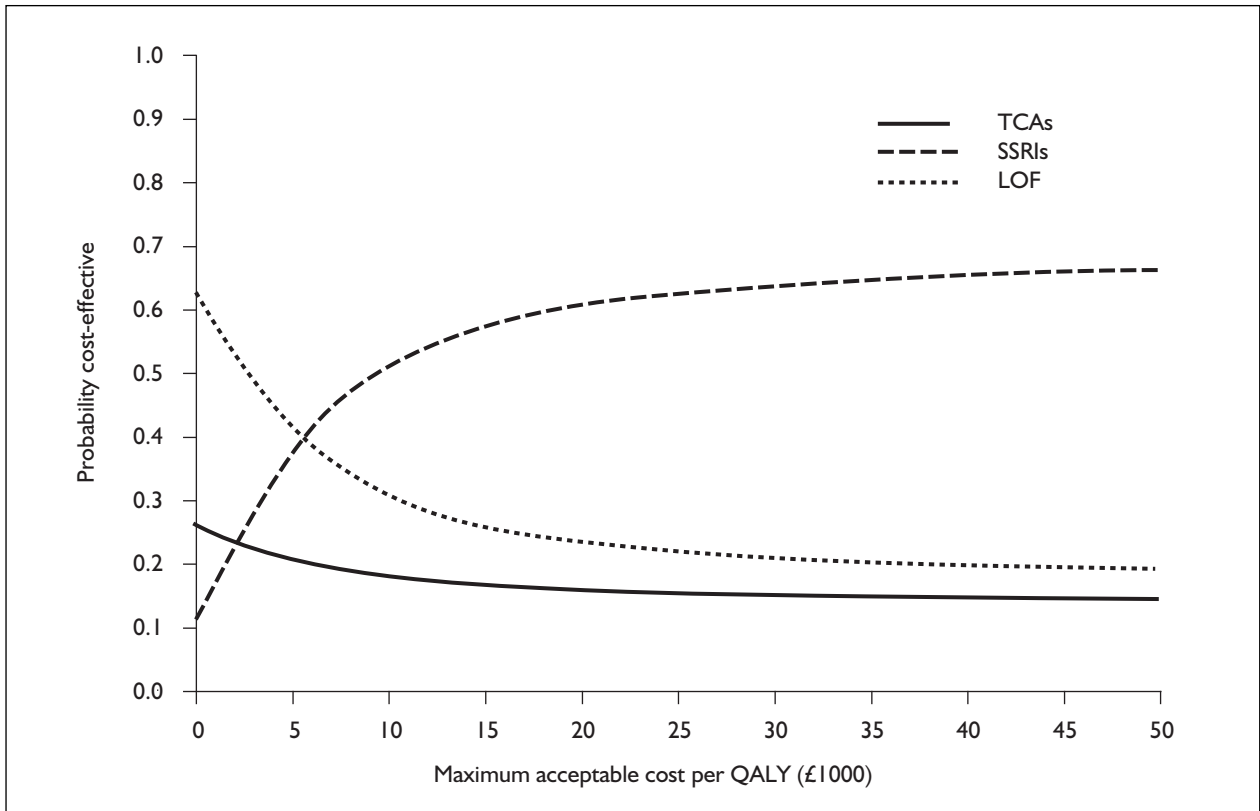


FIGURE 33 Cost-effectiveness acceptability curve (cost per QALY), using March 2003 prices to cost antidepressant drugs

TABLE 63 Summary of costs to 12 months from randomisation of patients with baseline CIS-R diagnosis of depression

	TCA (n = 85)	SSRI (n = 80)	LOF (n = 71)	All (n = 236 ^a)
Total costs				
Mean (SD)	£705 (£1181)	£934 (£1761)	£777 (£2109)	£805 (£1696)
Median	£354	£499	£362	£388
IQR	£205 to £585	£214 to £945	£204 to £578	£207 to £723

^a GP records were missing for three patients.

Chapter 6

Comment

Main findings

The main finding of the AHEAD trial was that there was no significant difference in the clinical effectiveness of the three classes of medication under investigation (TCAs, SSRIs and lofepramine), and the relative cost-effectiveness and cost-utility of the choice of the three classes appeared to be broadly similar. The only statistically significant finding related to clinical outcome was that patients allocated to lofepramine were more likely to switch treatment shortly after starting it than those allocated to the other classes. It also appeared that patients who received the treatment of their preference or that of their GP were less likely to switch. This finding is consistent with existing literature, mainly based on meta-analysis,²⁹ which suggests that in patients with this level of severity of depression the three classes of antidepressant are comparable in effectiveness, although possibly not in tolerability.

The analysis of costs to 1 year (based on GP records for all but three of the 327 patients randomised to the trial, and analysed on an ITT or intended strategy basis) shows that, at 2001 prices, antidepressant drugs cost an average of £71, which was only 8.5% of the total costs of these patients to the NHS during the year. Other drugs accounted for a further £114 (13.7%) of the mean total cost of £834. There were wide confidence intervals around these estimates, reflecting considerable between-patient variability, and the cost distributions were skewed. As a result, the differences in mean cost between patients in the three randomised arms of the trial, which suggest that the strategy of offering a TCA might be cheaper, were not statistically significant at a 95% level. However, neither was equivalence of costs demonstrated (at a maximum acceptable difference of 5% of log mean costs). This may well have been due to lack of power resulting from under-recruitment. Nevertheless, given that equivalence of costs was not proven, it was not appropriate to conduct a cost-minimisation analysis, but rather it was appropriate to estimate the joint density of cost and effect differences.¹¹⁵

In terms of cost-effectiveness, definitive interpretation is made difficult by the fact that all

the effectiveness data suffer from loss to patient follow-up. What is reassuring however is that the two measures of effectiveness (depression-free weeks and QALYs) both provide very similar pictures of comparative effectiveness.

Furthermore, the sensitivity analysis also indicates that the use of alternative cut-off values of HAD-D for depression-free weeks (with a cut-off of 8 in the main analysis and 11 in the sensitivity analysis) does not change the general picture. In all three analyses, differences in effectiveness are not statistically significant at a conventional level, but in each case superiority of SSRIs is suggested, with very little difference in effect between the TCA and LOF arms.

Plotting bootstrap estimates of cost per depression-free week or cost per QALY on a cost-effectiveness plane shows that in each analysis, and in each paired comparison of the three drugs, the bootstrap simulation estimates clearly occupy all four quadrants. This means that comparisons of mean cost-effectiveness ratios need to be interpreted with extreme caution and that CEACs provide the safest means of interpreting the results.

Based on the CEACs and within the considerable uncertainty resulting from the non-statistically significant differences and the very small absolute differences in measures of effect, the overall conclusion is that, if one places a value on a depression-free week in excess of £50–60, one can be 40–50% sure that the SSRI strategy is the most cost-effective of the three. As it is difficult to have a prior conception of what the appropriate value to the NHS of generating an additional depression-free week is, it is easier to consider the cost per QALY results. If one believes that an acceptable cost per QALY exceeds £5000–10,000, then one can be around 60% sure that SSRIs are the most cost-effective of the three strategies. Given that the National Institute for Clinical Excellence (NICE) operates with a benchmark of around £30,000, it seems safe to conclude that SSRIs are likely to be acceptably cost-effective.

If one were to place lower values on a depression-free week or QALY than these threshold points, then either the TCA or LOF strategy would be the

more cost-effective. The choice between these is very close. In the analyses of costs linked to effectiveness, LOF is the cheapest of the three strategies (except in the sensitivity analysis when the three most extreme patient cost outliers are removed): this is shown in the initial superiority of LOF on the relevant CEACs at zero or very low values for a unit of effect (i.e. at or close to the left-hand vertical axis). In the one sensitivity analysis removing outliers, and in the analysis of costs to 1 year, TCAs are cheapest. This comparison suggests that the cost-effectiveness choice between TCAs and LOF may be distorted by the incomplete follow-up of patients in terms of their assessment of effectiveness. On these data it would probably be unwise to distinguish between TCAs and LOF in terms of cost-effectiveness. These findings are broadly consistent with those of the only other prospective study, by Simon and colleagues.⁷⁹ They are also compatible with advice in the draft NICE guidance that SSRIs should be the first choice.¹¹⁶

Strengths and weaknesses of the study

The main principle informing the design of this study was to ensure its external validity, or generalisability, to the NHS context. The decisions to include a preference arm, to allow drug switching during the course of the study and to use ITT analysis all reflect this imperative. Inevitably, these refinements were made at some cost to the internal validity of the study. Thus, the main strengths of this work are that the study was carried out in a naturalistic setting and is highly likely to reflect usual clinical practice in most respects. It is important to remember that the intervention being investigated was the effect of the policy of choosing treatment, not the actual treatment delivery itself. The practices recruiting patients were drawn from a wide geographical area, and included rural and urban populations within a range of relative affluence. This local population has a relatively low prevalence of ethnic minority patients and results may not generalise to areas with a higher proportion of such patients. Difficulties in recruitment and the impossibility of checking completeness of referral make it difficult to be completely confident about the representativeness of the sample.

To investigate the representativeness of referred patients further the patients referred to this study were compared with patients recognised by their GPs to be depressed in the Hampshire Depression

Project (HDP),¹¹⁷ which was carried out in the same region of the UK and involved screening consecutive general practice attenders. The gender split was similar in the AHEAD sample (32.7% male, 67.3% female) to the patients recognised as depressed in the HDP sample (29.6% and 70.4%, respectively); however, more of the AHEAD sample were employed, self-employed or temporarily away from work (60.9%) than in the HDP sample (43.4%), and the AHEAD patients were somewhat younger (87.2% were aged 17–59 years) than the HDP sample (of whom 84.1% were aged 16–64 years). So there is some evidence suggesting referral bias, and it cannot be stated with certainty that these findings would generalise to the whole population of patients diagnosed with depression in UK primary care. Health service use is likely to be greater among older patients and among patients who are not in employment, and so this study may have underestimated total health service costs. This suggests, however, that antidepressant costs might be even smaller as a fraction of total health service costs among patients with depression in general, and therefore differences in costs between classes would be even less likely to contribute to a difference in overall cost-effectiveness, given the lack of difference in effectiveness between classes.

It is important to note that, as a result of the naturalistic design, most patients recruited had mild symptoms. Less than 30% had moderate or severe depressive episodes on the CIS-R, while nearly 40% had mixed anxiety and depression, and 14% had no identifiable psychiatric diagnosis. This is in line with other papers showing that antidepressants are often prescribed for mild depression,^{20,43,118} despite a lack of evidence that they are any more effective than placebo in such patients.

The assessment measures were chosen to be the best possible that were feasible for use in this context, and are regarded as the gold standard for this type of study. There is a trade-off between the use of interview measures and self-report measures: the former may yield data of higher quality, but at greater cost and inconvenience to both patients and researchers. The research team was often told by patients who no longer wished to participate that as they were now feeling well they found completing the questionnaires somewhat distressing.

The main weakness of the study was its failure to recruit to the sample size estimated by the power calculation; thus, power to detect differences

between the classes of antidepressant was limited. This failure may well have been linked to the requirement to allocate patients by remote randomisation, which created difficulties for the recruiting GPs and impaired the momentum of recruitment at the outset of the study. In this instance the internal validity of the study was improved at the cost of limiting external validity.

There is no doubt that the low recruitment also reduced the power to show equivalence or statistically significant differences in cost-effectiveness. Studies are, however, frequently not set up to be powered to show statistically significant differences in economic outcomes; indeed, many economists would argue that it should not be a question of testing a hypothesis, but of estimating cost-effectiveness and recognising the degree of uncertainty. Thus, cost-effectiveness ratios were estimated in terms of both cost per depression-free week and cost per QALY. The CEACs reflect the uncertainty. Hard-line estimators would argue that this uncertainty should effectively be ignored in a decision as to which alternative to use, which should be decided on the basis of which option has the highest probability of being cost-effective at their threshold of willingness to pay for an additional unit of effect. The uncertainty is the starting point for deciding whether it is worth collecting more information (typically using value of information analysis). The present conclusions favouring SSRIs seem fairly robust given all the data (including the sensitivity analyses, the expectations of further price falls, the data on switching, etc.). The overall 'sameness' of the cost-effectiveness data suggests that, even if with a larger sample size a statistically significant difference were found in outcomes or costs, it is unlikely that either would be so substantial as to suggest that there is a significant risk in acting on this evidence, rather than attempting to undertake another larger trial with all the difficulties that this would involve.

The duration of follow-up (1 year) was chosen to yield data of maximum relevance to decision-making. Shorter follow-up may have given a lower rate of attrition, but may also have missed important differences emerging over the longer course of illness. Attrition is always a problem for this type of longer term cohort study. It should be noted that only the clinical outcome data were compromised by attrition; cost data were available for almost all patients for a full year of follow-up. Great care was taken in the analysis to take account of this in such a way as to minimise possible bias. Sensitivity analyses were also

conducted to investigate possible sources of bias. Broadly speaking, the sensitivity analyses all support the conclusions drawn from the primary analyses.

Analysis of longitudinal studies with missing data

There is still debate about the optimum approach to analysis of 'censored' data such as these, when derived from a long-term follow-up study with inevitably high attrition rates. The usual approach of a 'last observation carried forward' or an ITT analysis tends to minimise differences between groups, and is not ideal when cost data are available for the whole period while clinical data are often missing.

In this study, the HAD-D score was measured at regular intervals, and the time for which the patient was below a fixed level was measured. If values were missing, but there were recorded values either side (so called intermittent dropout), then an interpolation could be carried out. If there were no observations after the first missing value (terminal dropout) then interpolation could not be carried out. One solution was to truncate the observations for an individual at the last observed value and compute the length of time for which a patient was not depressed up until that point. One could then conduct a weighted analysis of the proportion of time for which a patient was not depressed, weighted by the follow-up time. Thus, a patient followed up for 6 months, who was not depressed for 2 months, would have a score of 0.33 with a weight of 0.5. The score was not simply multiplied by the weight in the analysis; rather, the weight was used in the analysis.

Thus, weighted mean and variance are given by

$$\bar{x}_w = \frac{\sum w_i x_i}{\sum w_i} \text{ and } s_w^2 = \frac{\sum w_i (x_i - \bar{x}_w)^2}{\sum w_i - 1}.$$

Two disadvantages of this are that patients have differing lengths of follow-up, and potential information is ignored; for example, if a patient is truncated at 9 months but has had a HADS score of 1 for the last 6 months of follow-up, it is likely they will remain undepressed for all 12 months.

An alternative approach is to assume that the missing data are ignorable. This assumes that they are missing at random (MAR, see Chapter 4).¹⁰⁵ This model suggests that the probability of an observation being missing may depend on

previous values of the observation but, having allowed for these, not on the current (unobserved) value. The alternative is missing not at random (MNAR). Since, by definition, one cannot observe the current missing value, it is impossible to test for differences between MAR and MNAR. However, MAR is a plausible mechanism for longitudinal data, since there is a strong degree of autocorrelation in the data enabling prediction of missing values with reasonable certainty. Thus, an alternative analysis is to estimate the intermittent and terminal missing values assuming MAR and a model that includes treatment group using all available values of the HAD-D, and then do the same interpolation to find the time for which a person is not depressed, over the entire follow-up period. Various sensitivity analyses were carried out, and the results assuming MAR and the weighted analysis agreed closely.

The advantage of estimating the values using MAR is that no weighting is required, and since the results are interpolated to the full follow-up period, the results can be compared with the health economic data that apply to this period. It may possibly be more sensitive since it is incorporating more information in the analysis.

Validity of depression-free weeks as an outcome measure

The measure of 'depression-free weeks' was chosen because the use of such measures of effect is now fairly common in other clinical areas. For example, symptom-free days are now widely used and accepted for asthma studies, as demonstrated by Sullivan and colleagues.¹¹⁹⁻¹²¹

The use here was very much influenced by the use of the same measure (or at least depression-free days) in studies by Simon and colleagues.¹²²⁻¹²⁴

Although it is not possible to give a formal evidence-based assessment of the validity of depression-free weeks, on the basis of the data, it may be argued that the similarity of the shapes and the ordering of the three choices in the CEACs strongly suggest that depression-free weeks are closely correlated to QALYs.

Patient preference

The number of participants expressing a preference for one or other of the study arms in advance of randomisation was low, ranging from

12 out of 113 (11%, TCAs) to 15 out of 105 (14%, lofepramine). These numbers were much lower than figures reported in the literature, which suggested figures between 30 and 60%.^{65,125} However, in both of these earlier studies the preferences were largely in favour of psychological treatment, which was not available in this study. The present figures suggest that such strong preferences may not exist in a choice consisting only of differing drug treatments. Those small numbers expressing a preference may have been those with previous personal experience of treatment, or who had experienced such treatment through close family members or friends. A slightly greater number of patients did not receive the allocated treatment as a result of GP preference.

The study design may have increased recruitment by up to 14%, but the researchers cannot be sure that these participants would not have participated if the option to choose a preferred treatment had not been available, and the inclusion of this arm created a more complex trial design that in itself risked reducing recruitment. In addition, it is not possible to determine the extent to which preferences expressed in this study were representative of the views of depressed individuals whose GPs feel that treatment with antidepressants is appropriate. The extent to which these criticisms are applicable to any trial is dependent on the treatment options available within it. If the trial design had been used for an alternative treatment area, or involved a different choice of treatments, it may have had more beneficial effects on recruitment and degree of representativeness.

Patient recruitment

The principal difficulty in work of this type, encountered by the present group in previous primary care trials,^{117,126} is that of adequate patient recruitment. This is also the case in other centres, as demonstrated by Fairhurst and Dowrick.⁸⁴ In the UK general practice research is an 'add-on' activity, of considerably lower priority than patient care, and the time for supporting research activity that has to be poached from other activities is very limited. As a result, recruitment targets are dependent on the goodwill and cooperation of the primary care team and are very hard to meet. Initial enthusiasm for studies quickly wanes, and other priorities or other research endeavours displace the study in question. A study such as this, which provides no

additional benefits for the GP or their patient, will tend to be less successful in recruiting than one that offers benefits such as additional treatment or referral options. Measures to maintain practitioners' enthusiasm for the study, such as frequent visits by researchers to practices and the use of reminders or cues, are of only limited effectiveness. One way to manage this problem may be to involve practices in recruitment for a fixed and limited period, so the commitment is finite rather than open ended: this approach is being evaluated in this group's next study funded by the HTA programme (THREAD). Further suggestions are made in Chapter 7.

To maximise recruitment, procedures need to be as simple and time-efficient as possible. There is conflict, however, between this imperative and issues such as blinding of randomisation. The decision in this work to opt for remote randomisation was imposed externally, and may have led to lower recruitment than would have been possible with the original plan of using NCR envelopes. There is no doubt, however, that

remote randomisation is less subject to interference than on-site randomisation.

Clinical implications

It seems reasonable to conclude from the present study that patients and GPs should choose suitable treatments for depression on grounds other than tablet cost. Although the study has insufficient power to be absolutely confident in this recommendation, it appears that issues such as tolerability, safety and patient and doctor preference should take priority over cost alone. The fact that the newer drugs such as SSRIs are now approaching the end of their patent lives will bring down their costs, further diminishing the importance of this consideration. It is important to bear in mind that the evidence obtained in this study applies only to those patients receiving treatment in primary care, and cannot inform drug choice in other settings, such as patients with more severe depressive symptoms in outpatient or inpatient secondary care settings.

Chapter 7

Conclusions

Implications for healthcare

The principal conclusion from the present study is that differences in the overall costs of care when the first choice of antidepressant is made from one of the three categories studied are likely to be small. It therefore seems appropriate for policy to consider patient and doctor preferences, taking account of factors such as safety and tolerability, rather than primarily cost. Overall, tablet costs form only a minor part of the total costs of care (<10%).

It is difficult to see how a better study of this question could be conducted in UK primary care at present, given practical difficulties in recruitment, randomisation procedures and participant attrition. It is possible that greater statistical power could be achieved by repeating the work in a multicentre framework, but the present results do not provide much justification for doing this, since cost differences must be at best small, and the changing health economic environment resulting from price shifts would limit the longevity of any findings. The shelf-life of findings from any such study is limited by the fact that patents on existing products expire, pricing structures change and new products are brought to market.

Recommendations for research

Recruitment to trials in primary care remains a difficult problem to solve. The following strategies may be helpful and could be investigated further:

- financially rewarding recruitment to high-quality research studies [those funded by the partnership organisations, the Medical Research Council (MRC), NHS R&D and Association of Medical Research Charities], by giving practices points in the General Medical Services performance-related contract, which is to be revised in 2006
- funding nurse time in the practices, as in the MRC GP research framework
- using practitioners with a track record of recruiting to other studies
- working extensively with practitioners and support staff in a smaller number of practices, rather than stretching resources thinly over a large number of practices
- building in a pilot phase to test recruitment, and including qualitative interviews with patients, especially those declining to take part in the trial
- keeping the inclusion and exclusion criteria as brief and clear as possible
- keeping the information sheet as short as possible, but in keeping with giving enough information
- building IT support, including better e-mail links with practices, and a website with study information
- using pop-up screens on practice computers to remind practitioners to consider referral of patients with the relevant conditions.

Further research is still needed to address other important questions surrounding the management of depressive illness in primary care. First, there is still uncertainty about the optimum severity threshold at which medication should be used. There is concern that attempts to improve the sensitivity of GPs, that is to increase recognition rates, may have resulted in reduced specificity, that is inappropriate or unnecessary overtreatment of milder cases with a high spontaneous remission rate. A recent US review¹²⁷ suggests that evidence for efficacy of drug therapy may be less convincing than previously supposed. Thus, there may be a case for more radical studies of the benefits of treating milder depression with drugs. This topic forms the basis of a new study funded by the HTA programme and led by the present group in Southampton (THREAD). Others have also suggested that all future trials of antidepressant therapy should contain a placebo arm.¹²⁸

Second, existing research suggests that provision of guidelines and training alone is insufficient to improve recognition and quality of management. The implementation of structured depression management programmes may be of benefit¹²⁹ but, to date, evidence of benefit has only been obtained in the US Health Maintenance Organization setting, and it would be valuable to test the feasibility and effectiveness of adopting this model in the UK context.

Third, it is apparent that GPs' prescribing decisions are based not on severity alone, but on a wider range of other factors such as physical co-

morbidity and recent life events. The importance of such factors in prescribing decisions should be further investigated using a combination of qualitative and quantitative methods. The Southampton group is in the process of completing two such studies.

Fourth, the authors hope by further analysis of data to establish whether or not it is necessary in studies of this type to collect detailed cost data from patients, or whether data from GP records would suffice. This will be of value in planning future work. Future studies could also usefully explore alternative ways of collecting data, for example using telephone follow-up or payment for data.

Finally, it is apparent that one of the most important factors limiting effectiveness of treatment is the fact that many patients are reluctant to accept medication, and discontinue treatment early. Better understanding of the factors that give rise to this should lead to the development of strategies for improving treatment persistence by means of enhanced consultation skills and possibly additional forms of medication management or support. Although the development of such strategies is at an early stage, it is important that in due course these are subjected to evaluation in large pragmatic trials to test their efficacy.



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Contributions of the authors

Robert Peveler (Professor of Liaison Psychiatry) contributed to the design, application for funding, data collection and data analysis, and was lead author for the report. Tony Kendrick (Professor of Primary Medical Care) and Martin Buxton (Professor of Health Economics) contributed to the design, application for funding, data collection, data analysis and the drafting of the report. Louise Longworth (Research Fellow) contributed to the data analysis and the drafting of the report. David Baldwin (Senior Lecturer in Psychiatry) and Michael Campbell (Professor of Medical Statistics) contributed to the design, data

analysis and the drafting of the report. Michael Moore (General Practitioner) and Judy Chatwin (Research Assistant) contributed to the data collection, data analysis and the drafting of the report. Jonathan Goddard (Medical Statistician) contributed to the data collection and the data analysis of the study. Andrew Thornett (Research Fellow in General Practice) contributed to the data collection and the drafting of the report. Helen Smith (Reader in Primary Medical Care) contributed to the design of the study. Christopher Thompson (Professor of Psychiatry) contributed to the design and the application for funding for the study.



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Appendix I

Initial letter to GPs



University
of Southampton

AHEAD

School of Medicine

Community Clinical
Sciences Division

Prof C Thompson
Mental Health
Prof T Kendrick
Primary Care

*Assessing Health Economics
of Antidepressants (Ahead)*

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Dr Andrew Thornett.
Clinical Research Fellow
Tel. 02380 825067

March 2000

Dear Doctor,

Are the newer SSRI antidepressants more cost-effective than the older tricyclics?

Prescribing of the newer selective serotonin reuptake inhibitors has increased rapidly in UK general practice throughout the 1990s. One reason is the perception that SSRIs are easier to take and are not needed to be discontinued because of side-effects as often as with tricyclics.

However, analysis of clinical trials paints a different picture. SSRIs appear to be no more effective than the tricyclics, only marginally better tolerated, and there is not a significant difference in discontinuation rates.

It has been estimated that, if we switched over completely to SSRIs, the NHS antidepressant drug budget would increase from £90 million to around £250 million per year. The health economists insist that tricyclics should remain the first choice of treatment for depression in primary care (Hotopf et al, Br J Psychiatry, 1996), but the patients included in the clinical trials are a select group which may not be representative of all the patients treated in general practice.

The question of whether the SSRIs are better tolerated than the tricyclics, and therefore potentially more cost-effective, is therefore an important one to answer. It needs to be addressed by a trial in general practice, which includes **all** patients needing antidepressant treatment. We would like your help to carry out this study. The attached sheet outlines the AHEAD study in more detail.

If you and some of your partners would like to meet with a member of the research team to discuss the project further please could you contact the Clinical Research Fellow, Dr Andrew Thornett, on 02380 825067, fax on 02380 825538, or alternatively e-mail eanador@soton.ac.uk.

This important study has been funded by the NHS R&D Programme and is not a drug company trial.

Many thanks in anticipation of your continuing help.

Yours sincerely

Professor Chris Thompson
Professor of Mental Health

Professor Tony Kendrick
Professor of Primary Medical Care



A randomised comparative trial to compare the cost effectiveness of tricyclic antidepressants, lofepramine and SSRIs

Why is the trial needed?

Antidepressant prescribing currently costs the health service £88 million per annum. A growing proportion of this is attributed to newer antidepressants. It has been estimated that if all patients were switched to SSRIs the bill would grow to £250 million. It has been suggested however that such a switch may be cost effective because of improved compliance, rapid recovery and reduced use of specialist care. This study aims to clarify this issue.

The aim of this study is to evaluate the use of health services and the economic consequences of the prescribing decision in the year following the initial prescription. The study will provide important information to inform cost effective prescribing.

The funding for the project has now been secured and we are now able to begin recruitment of practices. Ethical committee approval has also been given for the whole of Hampshire (ethics committee numbers: North & Mid-Hampshire 038/A; Southampton & SW Hants 029/98; Portsmouth & SE Hampshire 02/99/803).

How many patients are needed?

We need 900 patients and the involvement of 40 GPs to recruit patients over eighteen months.

Will I have to follow complex diagnostic procedures?

No. The trial aims to evaluate current practice. We want you to include all patients who are depressed and for whom you consider antidepressants to be appropriate therapy. Accurate diagnostic information will be obtained by structured psychological interview carried out by a researcher shortly after the initial prescription.

Will my prescribing be restricted?

There is some choice within therapeutic groups. We have included three tricyclic antidepressants, amitriptyline, imipramine and dothiepin. Three SSRIs are included: fluoxetine, sertraline and paroxetine. Lofepramine is also included. These drugs represent 90% of antidepressants prescribed.

What if the patient does not want a particular drug?

The design is a randomised comparative trial taking into account patient and doctor preference. This means that all patients with depression should be included unless they refuse any kind of follow-up. Once patients have agreed to follow-up they will be randomised to one of the three drug groups. If the patient or the doctor has strong preferences then these may be taken into account. All patients whether included in the randomised trial or the preference arm will be followed up. This design has been chosen because it takes into account preferences which may themselves influence outcome and should also improve generalisability of the results because the large majority of the patients treated are included in the study.

What is the extra work I will need to do?

We are asking GPs to recruit patients for the study. The extra work takes about 5 minutes and involves asking the patient whether they would be happy to see a researcher who would discuss the study with them. One of the research team would then telephone the patient at home and go through the consent process. If the patient is happy to take part then we will fax a treatment allocation sheet to the practice so that a prescription can be generated. We then ask you to continue to care for the patient in much the same way as you would do normally.

How much will practices be paid?

£13 per patient. This includes an allowance for clerical help in pulling medical records for inspection at the end of the trial period. The fee will be paid for all patients consenting to take part in the study and will include patients in both the randomised and patient preference arms.

What do the patients have to do?

They have to agree to see a researcher who will undertake a structured interview to obtain accurate diagnostic information and a further interview after three months. They will be asked to complete 7 questionnaires about their use of health and social services together with three-monthly psychological and quality of life instruments to assess recovery over one year. Patients will also be asked to consent to their notes being reviewed at the end of the trial for confirmation of service usage and medications prescribed.

What to do if you would like to know more

You can still participate in the AHEAD study even if not all the partners in your surgery would like to do so. If you and some of your partners would like to meet with a member of the research team to discuss the project further please could you contact the Clinical Research Fellow, Dr Andrew Thornett, on 02380 825067, or the AHEAD team on tel./fax 02380 825538, or alternatively e-mail eanador@soton.ac.uk.

Appendix 2

Eligibility criteria



Eligibility Criteria

INCLUSION

You have diagnosed the patient to be:

- Suffering from a new episode of depression.
- Suitable for treatment with antidepressant medication (include older adults and patients with co-morbid physical and mental disorders) with language skills adequate to participate.

EXCLUSION

Your patient can be included provided they

- Do not clinically require urgent treatment with antidepressants prior to the next appointment.
- Have not been prescribed antidepressants during the past month.
- Are not under 18 years of age, pregnant, breast feeding, suffering from a confusional state, terminally ill, or have a condition contraindicating the use of antidepressants.
- Are not temporary residents.

TREATMENT GUIDELINES

The instructions will be given as the starting dose followed by a recommended escalation schedule **unless recovery from depression or intolerable side effects intervene.**

• Tricyclics

Age 18–65 50 mg rising in 25-mg weekly steps to 150 mg

Age 65+ 25 mg rising in 25-mg weekly steps to 125 mg

• SSRIs

Fluoxetine – 20 mg single dose throughout the study.



Paroxetine – 20 mg increasing to 30 mg after 3 weeks and 40 mg after 6 weeks.

Sertraline – 50 mg increasing after 3 weeks to 100 mg and after 6 weeks to 150 mg (not to treat with 150 mg for > 8 weeks)

• Lofepramine

70 mg rising in weekly 70-mg increments to 280 mg

***IF** first line treatment fails treatment may be changed as clinically indicated.

***If possible continue** full dose for 6 months after depression decreases, or continue to end of 1 year study period if the patient has previously suffered two attacks within the last 5 years.

Appendix 3

Patient information sheet I



University
of Southampton

AHEAD

School of Medicine

Community Clinical
Sciences Division

Prof C Thompson
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Prof T Kendrick
Primary Care

*Assessing Health Economics
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Please tear out and give to the patient to take home

AHEAD Research Study

Patient Information Sheet I

Please read this, you are welcome to take it away with you. Please remember that you have the right to decline to participate in the study at any time.

Your doctor has discussed the problems you have been having and believes you have an illness called depression. Depression usually improves when treated with antidepressant tablets. There are many kinds of depression tablets to choose from, most of which are equally effective. Your doctor is one of several who are taking part in a research study of 900 patients to try to find out which tablet represents best value for money for the NHS.

We would be very grateful if you were to agree to help us with this. We would like to follow your progress while taking one of three kinds of medicines (*tricyclics, SSRI and tricyclic like medicines*). About three-quarters of the people who already take antidepressants will be taking one of the three groups of tablets used in our study, so they are very commonly used. Because we do not know which treatment gives best value for money we need to make comparisons. People will be put into groups and compared. Which group they are in is chosen as if by the toss of a coin, although the choice is actually made by computer. The researcher will phone a special number to find the treatment allocation. Each group has a different treatment and there is a 1 in 3 chance of being allocated to one of the three types of antidepressant. However, if you don't want to have the treatment you are allocated, you will still be able to choose another type of antidepressant and stay in the study.

We will be able to give you some more information about the drugs if you agree to participate but at this stage please let us know if you would agree to the following:

- a) To be interviewed by the researcher either in your home or at a venue that is most convenient to you, now and again in approximately three months. The interview will not usually last more than 60 minutes and will involve answering a number of questions about how you are feeling. The information is fed directly into a computer but the researcher will help with this.
- b) To complete some questionnaires with the researcher. They will help you to fill in the forms if you have any difficulties. We would then send you the same questionnaires by post every month for three months and then every quarter for the following nine months. The questionnaires will establish which

NHS services you have been using and how you are now feeling. The questionnaires take approximately 20 minutes in total to complete. You will also be given a diary sheet on which to record any contacts you may have had with any health or other care services and a record sheet on which to list any medication or interventions that you may be using.

- c) If you agree to take part we would also like to use some information from your general practice records to see how many times you needed medical care during the study. This information will be treated in the strictest confidence and no one outside the surgery will know your identity. However, if you withdraw from the study then your records will not be accessed.

If you do not wish to take part in this study it will not stop your doctor from giving you the treatment he or she thinks you need. If you do agree, you would be free to withdraw from the study at any time.

The study will continue for one year and we would like you to complete all the questionnaires even if your treatment is changed or you stop treatment altogether. All the drugs are currently in use so if you still need medication at the end of the trial period your doctor will be able to continue with your prescription.

All the information which is collected about you will be kept strictly confidential. Any information about you will be anonymised so that you cannot be recognised from it. If the researcher is very concerned about your health they may inform your own family doctor about their concerns, but this would be very unusual and only after discussing it with you.

The only disadvantage to you to participating in the study will be the time taken to complete the questionnaires. There are no experimental drugs being used. All the drugs may have some side effects which are detailed on a separate information sheet. The benefit of participating would be to help doctors in the future choose drugs which represent best value for money for the NHS.

Please complete the attached form indicating if you prefer one of the treatments and hand it back to the researcher.

If you do agree to take part in this study then the researcher will interview you at home or at a mutually agreed venue, if this is not convenient. Following this interview you will be given some more information about the tablets before you start your treatment.

If at any stage you have any further questions about the study then please contact Julia MacLeod, Judy Chatwin, or Andrew Thornett on:

02380 825542

Your own doctor remains responsible for your treatment and any questions about the treatment or side effects should be directed to him/her.

Appendix 4

Patient consent form I



University of Southampton



School of Medicine

Community Clinical Sciences Division

Prof C Thompson
Mental Health
Prof T Kendrick
Primary Care

Assessing Health Economics of Antidepressants (Ahead)

University of Southampton
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Tel +44 (0)23 80 825542
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Patient Consent I **Booklet ID** **Practice ID**

Your doctor has discussed the problems you have been having and believes you have an illness called depression. Depression usually improves when treated with antidepressant tablets. There are many kinds of depression tablets to choose from, most of which are equally effective. Your doctor is one of several who are taking part in a research study to try to find out which tablet represents best value for money for the NHS.

We would be grateful if you were to agree to help us with this. We would like you to see a researcher who will talk through the study with you and obtain your consent if you agree to take part. There is no obligation to take part, and by signing this form you only agree to allow your doctor to give your contact details to the research team (Julia MacLeod, Judy Chatwin, Andrew Thornett).

Please note that you have the right to refuse to participate in the study or to withdraw at any stage after you have agreed to take part; this will not affect the care you receive from your doctor, who will continue to care for you as normal.

Patient's name

Address

Phone number

Patient's signature

GP's signature Date

Print name

Please tick appropriate box below:

I have arranged to see this patient again on (date)

I intend to issue the prescription without seeing the patient again. This needs to be issued by

Please fax this form and the following two pages to the research team on (023) 8082 5538 or (023) 8023 4243.

Appendix 5

GP contraindication form

Booklet number

Today's date - -

TO BE COMPLETED BY THE DOCTOR:

Please sign **ONLY ONE** of the two statements below.

I am happy for this patient to be prescribed a medication from any one of the three antidepressant groups used in this study, as listed below.

SSRI	Tricyclic	Lofepramine
Signed.....	Date.....	

I am **NOT** happy for this patient to be prescribed a medication from the group or groups I have indicated below (*tick box where applicable*):

SSRI <input type="checkbox"/>	Tricyclic <input type="checkbox"/>	Lofepramine <input type="checkbox"/>
Signed.....	Date.....	

Please state the main reasons why you do not wish this patient to receive a medication from any of the groups (*please list all that apply*):

(*please state*)

.....

Is the patient suffering from any co-morbid disorder that the research team needs to be aware of?

Has the patient been treated with an antidepressant before: **Yes:** **No:**

If yes, please tick all classes that have previously been used:

SSRI: **Tricyclics:** **Lofepramine:**

Other (*please state*):

Appendix 6

GP preference if patient not in study

Booklet number

Today's date - -

If this patient was not participating in the AHEAD trial, which type of antidepressant would you have prescribed to initiate treatment?

Please tick the group of choice and the drug of preference below:

- | | | | |
|----------------------------------|--------------------------|--|--------------------------|
| 1) Tricyclic | <input type="checkbox"/> | Amitriptyline (<i>Lentizol, Tryptizol</i>) | <input type="checkbox"/> |
| | | Dothiepin (<i>Prothiaden</i>) | <input type="checkbox"/> |
| | | Imipramine (<i>Tofranil</i>) | <input type="checkbox"/> |
| 2) SSRI | <input type="checkbox"/> | Fluoxetine (<i>Prozac</i>) | <input type="checkbox"/> |
| | | Paroxetine (<i>Seroxat</i>) | <input type="checkbox"/> |
| | | Sertraline (<i>Lustral</i>) | <input type="checkbox"/> |
| 3) Tricyclic related | <input type="checkbox"/> | Lofepramine (<i>Gamanil</i>) | <input type="checkbox"/> |
| 4) Other (<i>please state</i>) | | | |

How strongly do you prefer this medication for this patient?

Very strongly Strongly Moderately Mildly Very mildly

Can you say why you prefer this class of medications? *Please list all reasons.*

(*Please state*)

.....

.....

.....

.....

Appendix 7

Patient consent form II



University of Southampton



School of Medicine
Community Clinical Sciences Division

Prof C Thompson
Mental Health
Prof T Kendrick
Primary Care

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Consent Form II

Randomization number

Date --

Please tick box

- I confirm that I have read and understood Information Sheet I
- I understand my participation is voluntary and I am free to withdraw at any time without my medical care or legal rights being affected
- I am willing to allow access to medical records held by my GP but understand that strict confidentiality will be maintained
- I agree to information from my medical records being used in the study
- Further information about the drugs will be provided but this does not commit me to taking the allocated drug
- I consent to see the researchers and complete the questionnaires

Signed

Name (please print in full).....

Date of birth

Date

Signature of Researcher

Please leave top copy in the booklet, tear out and give one copy to the patient and send one copy to GP in envelope

Appendix 8

Patient information sheet 2



University
of Southampton

Ahead

School of Medicine

Community Clinical
Sciences Division

Prof C Thompson
Mental Health
Prof T Kendrick
Primary Care

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Patient Information Sheet 2 (Lofepramine)

You have already seen the information sheet and agreed to help us with this study. We have chosen one of the three groups, which we would like you to have as your antidepressant treatment. You have been allocated to one type of treatment. These tablets are called:

Lofepramine

A full information sheet about the tablets is available for you to read and take away with you.

If you prefer not to take these (for whatever reason) or if you or your doctor know of a medical reason why you should not take them, you will be prescribed an alternative tablet but we would still like to see you for the interview and questionnaires.

Please remember you are free to withdraw from the study at any time and this will not affect the care you receive from your doctor.



University
of Southampton

Ahead

School of Medicine

Community Clinical
Sciences Division

Prof C Thompson

Mental Health

Prof T Kendrick

Primary Care

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(2a) Information sheet for patients prescribed lofepramine

Lofepramine (Gamanil) 70mg

Antidepressants may not make you feel less depressed for the first two or three weeks of taking them. Please keep taking them until the doctor tells you to stop.

Before you start taking lofepramine, please check the following:

You must tell your pharmacist or doctor if the answer to any of the following questions is YES. It may be necessary to give you another medicine or change the dose.

- Are you allergic to lofepramine, or tricyclic antidepressants such as clomipramine and imipramine?
- Are you pregnant, planning to become pregnant or breast-feeding?
- Do you have liver or kidney problems?
- Do you suffer from any heart problems, including irregular heart rhythms, or have you recently had a heart attack?
- Do you suffer from glaucoma, hyperthyroidism (overactive thyroid) or prostatic hypertrophy (overgrowth of the prostate gland)?
- Do you suffer from any blood problems or porphyria?
- Do you have a history of epilepsy or recent convulsions?
- Are you taking or have taken any other medicine such as monoamine oxidase inhibitors for your depression within the last 14 days?
- Are you taking any other medicines prescribed by your doctor, particularly certain drugs for asthma, decongestants, and sedatives including barbiturates, thyroid hormones or drugs to lower blood pressure?

This medicine may cause drowsiness. If affected do not drive or operate machinery. Avoid drinking alcohol whilst taking this medicine.

If in doubt, talk to your pharmacist.

If you go into hospital to have an operation, tell the anaesthetist or other medical staff that you are taking Lofepramine.

Instructions for taking your medicine

Follow your doctor's directions.

Check the label to see how often you should take your tablets. Your pharmacist will help if you are not sure.

Swallow the tablets whole with a drink of water or milk.

Make sure you do not run out of your tablets.

Do not stop taking your tablets without talking to your doctor first. In some cases, it may be necessary to stop taking your medicine gradually.

You should take adequate contraceptive precautions whilst taking these tablets. Inform your doctor immediately if you think you may be pregnant.

What if you take too many?

If you accidentally take too many tablets, tell your doctor at once. If you can't do this, go to the nearest hospital casualty department. Take along the tablets that are left, the container and the label so that the hospital staff can easily tell what medicine you have taken.

What if you miss a dose?

If you forget to take a dose, take it as soon as you remember, then go on as before. Never double up on the next dose to make up for the one missed.

Side-effects

As with most medicines Lofepramine can sometimes cause side-effects, which can include low blood pressure, fast heart rate, dizziness, drowsiness, agitation, confusion, headache,

malaise, nausea and vomiting, skin rashes and allergic skin reactions, increased sensitivity to the effects of sunlight, pins and needles, dryness of mouth, constipation, visual disturbances, difficulty in urinating, sweating and tremor.

On **RARE** occasions side-effects may include interference with sexual function, worsening of depression, mood swings and convulsions. There have been reports of blood disorders which may be characterised by fever or chills, sore throat, ulcers in your mouth or throat, unusual tiredness or weakness, unusual bleeding or unexpected bruises. Lofepamine may also cause liver problems, which may lead to a yellowing of the skin and whites of the eyes. Tell your doctor immediately if you notice any of these symptoms.

Do not be alarmed, most people take lofepramine without any problems.

If you think your medicine may be causing any problems, talk to your pharmacist or doctor.

How to store lofepramine

- Do not take the tablets after the "Use by" date. Keep them in their original pack.
- Store in a dry place. Protect from light.
- Keep all medicines out of reach of children, preferably in a locked cupboard.

Remember this medicine has been prescribed for you. Do not give it to anyone else as it may harm them even if their symptoms appear to be the same.

If your doctor decides to stop treatment, return any leftover tablets to your pharmacist. Only keep them if your doctor tells you to.

If you have any questions or are not sure about anything, ask your pharmacist or doctor. They can obtain additional information about this medicine if necessary.

If your doctor knows of any reasons why you should not take these tablets she/he will recommend an alternative.

Please remember you are free to withdraw from the study at any time and this will not affect the care you receive from your doctor.

Patient Information Sheet 2 (Tricyclics)

You have already seen the information sheet and agreed to help us with this study.

We have chosen one of the three groups, which we would like you to have as your antidepressant

treatment. You have been allocated to one type of treatment. These tablets are called:

Tricyclics

There are three different Tricyclic antidepressants to choose from. With the help of your doctor you may take any one of the following:

Amitriptyline Dothiepin Imipramine

A full information sheet about the tablets is available for you to read and take away.

If you prefer not to take any of these (for whatever reason) or if you or your doctor know of a medical reason why you should not take them, you will be prescribed a more suitable tablet but we would still like to see you for the interview and questionnaires.

Please remember you are free to withdraw from the study at any time and this will not affect the care you receive from your doctor.

(2a) Information sheet for patients prescribed tricyclics

(Amitriptyline, Imipramine or Dothiepin)

Antidepressants may not make you feel less depressed for the first two or three weeks of taking them. Please keep taking them until the doctor tells you to stop.

Before you start taking tricyclics, please check the following:

If you answer yes to any of these questions, you should not take tricyclics. Talk to your doctor or pharmacist at once. It may be necessary to give you another medicine or change the dose.

- Have you ever had a reaction to any tricyclic antidepressants?
- Are you pregnant, trying to become pregnant or breast-feeding?
- Do you have any diseases of the liver, heart or blood vessels?
- Do you have a history of being unable to pass urine?
- Do you have porphyria (too much of natural substances called porphyrins), epilepsy, an overactive thyroid gland, glaucoma (too much pressure inside the eyeball) or symptoms of an enlarged prostate gland (difficulty and increased frequency of passing urine)?

- Have you taken any antidepressants of the type known as monoamine oxidase inhibitors within the last 14 days?
- Do you have schizophrenia or symptoms of mania (great excitement or elation)?

Instructions for taking your medicine

Follow your doctor's directions.

Check the label to see how often you should take your tablets. Your pharmacist will help if you are not sure.

Swallow the tablets whole with a drink of water or milk.

Make sure you do not run out of your tablets.

Do not stop taking your tablets without talking to your doctor first. This sometimes leads to withdrawal symptoms such as perspiration, nausea, headache, being irritable or being unable to sleep.

You should take adequate contraceptive precautions whilst taking these tablets.

Inform your doctor immediately if you think you may be pregnant.

While you are taking tricyclics

- Tricyclics may react with some other medicines, including medicines you can buy without a prescription, for example cough and cold remedies. Always make sure your doctor, dentist and pharmacist know you are taking tricyclics. They may react with the following types of medicine:
- Medicines such as adrenaline (which your doctor or dentist may use with local anaesthetics), ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (which is in some cold remedies)
- Medicines with similar side effects to tricyclics
- Some medicines for treating high blood pressure may be less effective while you are taking tricyclics. These include guanethidine, methyl dopa and clonidine.
- Thyroid medications and disulfiram
- Cimetidine (for stomach ulcers, heartburn, excess stomach acid and indigestion)
- Barbiturates may decrease the effect of tricyclics and methylphenidate may increase its effect. Barbiturates, alcohol and any other drug which makes you drowsy will also increase the drowsiness caused by tricyclics.

Make sure your doctor knows you are taking tricyclics if you are going to have electroconvulsive therapy (ECT) or an operation. Special care is needed for both of these.

- Do not stop taking tricyclics suddenly unless your doctor tells you to. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take two doses at the same time.
- If you accidentally take too many tablets, tell your doctor at once. If you can't do this, go to the nearest hospital casualty department. Take along the tablets that are left, the container and the label so that the hospital staff can easily tell what medicine you have taken.

Side-effects

Tricyclics can sometimes cause side-effects. These may include:

- Drowsiness. This is quite common to start with but usually wears off. If you feel drowsy or unable to concentrate, do not drive or operate dangerous machinery. Do not drink alcohol as this will make the drowsiness worse.
- Anticholinergic effects: perspiration, dry mouth, blurred vision, dilated pupils, constipation, increased pressure inside the eyeball, difficulty in passing urine or high fever (especially when given with other anticholinergic or neuroleptic drugs).

RARE side-effects

- Effects on the heart and blood vessels: low blood pressure (leading to dizziness or fainting when standing up or sitting up quickly), high blood pressure, a fast heart rate, palpitations (thumping heart), stroke, heart attack and changes in the rhythm of the heart.
- Effects on the blood: a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting). The first signs you might notice could be bruising, bleeding, fever, pallor or sore throat.
- Effects on the nervous system: delusions, hostility or mania may become worse. Confusion, loss of concentration, disorientation (not knowing where you are), hallucinations, excitement, anxiety, restlessness, drowsiness, being unable to sleep, nightmares, numbness, loss of feeling and tingling at the extremities, loss of coordination, loss of control over movement, tremor (shakiness), coma, fits, changes in the pattern of brain recording, involuntary movements, difficulty in speaking,

dizziness, weakness, fatigue, ringing in the ears and headache.

- Allergic effects: rash, sensitivity to sunlight, urticaria (a puffy rash with weals similar to nettle rash) and swelling of the face and tongue.
- Effects on the digestive system: nausea, discomfort in the stomach, vomiting, decreased or increased appetite, weight loss or gain, sore mouth, black tongue, unpleasant taste, swollen salivary glands and diarrhoea. Part of the intestine (gut) becoming paralysed. This may lead to bad constipation, a swollen stomach, fever and vomiting.
- Rarely, damage to the liver which may lead to jaundice.
- Effects on glands and hormones: swollen testicles, sore or enlarged breasts, breasts unexpectedly producing milk, increase or decrease in sex drive, impotence, loss of sexual function, increased levels of blood sugar and passing small volumes of concentrated urine.
- Other: swollen ankles, the need to pass urine frequently and hair loss.

If you get any of these, or any other unusual effects, tell your doctor or pharmacist at once.

Do not be alarmed, most people take tricyclics without any problems.

How to store tricyclics

- Keep the tablets in a dry place at normal room temperature.
- Remember, as with all medicines, to keep tricyclics well away from children.
- Do not take the capsules after the expiry date on the package.
- If your doctor decides to end your treatment, return the leftover tablets to your pharmacist. Only keep them if your doctor tells you to.

If your doctor knows of any reasons why you should not take these tablets she/he will recommend an alternative.

Please remember you are free to withdraw from the study at any time and this will not affect the care you receive from your doctor.

Patient Information Sheet 2 (SSRIs)

You have already seen the information sheet and agreed to help us with this study.

You have been allocated to one type of treatment. These tablets are called:

SSRIs

There are three different SSRI antidepressants to choose from. With the help of your doctor you may take any one of the following:

Fluoxetine Sertraline Paroxetine

A full information sheet about the tablets is available for you to read and take away.

If you prefer not to take any of these (for whatever reason) or if you or your doctor know of a medical reason why you should not take them, you will be prescribed a more suitable tablet but we would still like to see you for the interview and questionnaires.

Please remember you are free to withdraw from the study at any time and this will not affect the care you receive from your doctor.

(2a) Information sheet for patients prescribed SSRIs

(Paroxetine, Fluoxetine or Sertraline)

Antidepressants may not make you feel less depressed for the first two or three weeks of taking them. Please keep taking them until the doctor tells you to stop.

Before you start taking SSRIs

You must tell your pharmacist or doctor if the answer to any of the following questions is YES. It may be necessary to give you another medicine or change the dose.

- Have you ever had an allergic reaction (which may include rash, itching or shortness of breath) to any SSRI before?
- Do you have kidney or liver trouble?
- Are you pregnant or could you be?
- Are you breast-feeding?
- Are you taking, or have you recently taken any medicines known as monoamine oxidase inhibitors (MAOIs)? MAOIs do not mix with SSRIs, so if you are taking any MAOI, or stopped taking them within the last 2 weeks, you must not take SSRIs.
- Do not take any MAOIs for at least 5 weeks after stopping SSRIs.
- Do you have epilepsy or diabetes?
- Are you taking, or have you recently taken, tryptophan?

- Are you taking, or have you recently taken, any other medicines?

Antidepressants can affect your judgement or coordination. Do not drive or use machinery unless you are sure that you are not affected.

Instructions for taking SSRIs

Follow your doctor's instructions. Check the label for how many tablets to take and how often to taken them.

- Swallow the tablets whole with a drink of water.
- Keep taking them until your doctor tells you to stop. Do not stop without telling your doctor first.
- Do not take more tablets than your doctor tells you to.
- If you miss a dose, take one as soon as you can. Then go on as before.
- You should take adequate contraceptive precautions whilst taking these tablets. Inform your doctor immediately if you think you may be pregnant.
- If you accidentally take too many tablets, tell your doctor at once. If you can't do this, go to the nearest hospital casualty department. Take along the tablets that are left, the container and the label so that the hospital staff can easily tell what medicine you have taken.

Side-effects

- Nervous system: headache, nervousness, sleeplessness, muscle tremor, anxiety, drowsiness.

- Digestive system: nausea, diarrhoea.
- Skin: sweating, itching. If you get a skin rash, stop taking the capsules at once and tell your doctor.
- Whole body: weak feeling.
- Respiratory system: shortness of breath.
- Poor sexual performance.
- You may lose a little weight.

These are usually nothing to worry about and go away after the first few weeks while you are taking SSRIs. If you are at all worried, tell your doctor.

Do not be alarmed, most people are able to take SSRIs without any problems.

How to Store Your Medicine

Do not take SSRIs after the use before date. Keep your tablets at room temperature, in a dry safe place and where children cannot see or reach them. Your tablets could harm them. If your doctor tells you to stop taking the tablets we suggest any remaining tablets should be taken back to the pharmacist who will dispose of them safely. Only keep the tablets if your doctor tells you to.

If your doctor knows of any reasons why you should not take these tablets she/he will recommend an alternative.

Please remember you are free to withdraw from the study at any time and this will not affect the care you receive from your doctor.

Appendix 9

Patient consent form III



University of Southampton



School of Medicine
Community Clinical Sciences Division

Prof C Thompson
Mental Health
Prof T Kendrick
Primary Care

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Consent to treatment allocation (Consent III)

Patient to complete

Randomisation number

Have you read Information Sheet 2 and 2a about the tablets we would like you to take?

Yes No (circle one)

Do you agree to take these tablets?

Yes No (circle one)

If you circled "No", it would help us if you could say why you don't want to have these particular tablets. Please put your comments below, but there is no obligation for you to do so.

.....
.....

Signed.....

Date.....

Name & address.....
.....

We would like to thank you for your participation in this study. Please note that you have the right to refuse to participate in the study or to withdraw at any stage after you have agreed to take part, this will not affect the care you receive from your doctor, who will continue to care for you as normal.

Signature of Researcher

Please leave top copy in the booklet, tear out and give one copy to the patient and keep one copy in your notes.

Appendix 10

Fax back to GP informing of randomisation



Assessing Health Economics of Antidepressants (AHEAD) Study
Tel: (023) 8082 5542

Date of researcher visit: --

Dear Dr

This patient has agreed to take part in the AHEAD study, and a copy of the consent form is enclosed for your records. The following study number has been assigned:

Randomisation number

Patient name:
Address:
Post code:

The allocated drug class from the randomisation process is marked below:

SSRI Tricyclic Lofepamine

- You did not say previously that this class was contraindicated and **the patient has agreed to take this medication.**
- We would like you to choose an appropriate medication either from those below or any other of your choice.
- Please tick the box below that corresponds with your choice.

<input type="checkbox"/> Fluoxetine	<input type="checkbox"/> Amitriptyline	<input type="checkbox"/> Lofepamine
<input type="checkbox"/> Paroxetine	<input type="checkbox"/> Dothiepin	
<input type="checkbox"/> Sertraline	<input type="checkbox"/> Imipramine	

If you have elected to prescribe another drug please state which

.....

Starting dose mg

Signed Date:

**Please return this form by faxing it back to the research team on:
(023) 8082 5538 or (023) 8023 4243.**



Assessing Health Economics of
Antidepressants (AHEAD) Study
Tel: (023) 8082 5542

Date of researcher visit: --

Dear Dr

This patient has agreed to take part in the AHEAD study, and a copy of the consent form is enclosed for your records. The following study number has been assigned:

Randomisation number

Patient name: _____
Address: _____
Post code:

The allocated drug class from the randomisation process is marked below:

SSRI Tricyclic Lofepamine

- You previously said that this class was **not contraindicated. However, the patient prefers not to take this medication.**
- We would like you to choose an appropriate medication either from those below or any other of your choice.
- Please tick the box below that corresponds with your choice.

<input type="checkbox"/> Fluoxetine	<input type="checkbox"/> Amitriptyline	<input type="checkbox"/> Lofepamine
<input type="checkbox"/> Paroxetine	<input type="checkbox"/> Dothiepin	
<input type="checkbox"/> Sertraline	<input type="checkbox"/> Imipramine	

If you have elected to prescribe another drug please state which
.....

Starting dose mg

Signed Date: --

**Please return this form by faxing it back to the research team on:
(023) 8082 5538 or (023) 8023 4243.**



Assessing Health Economics of Antidepressants (AHEAD) Study
Tel: (023) 8082 5542

Date of researcher visit: □□-□□-□□

Dear Dr

This patient has agreed to take part in the AHEAD study, and a copy of the consent form is enclosed for your records. The following study number has been assigned:

Randomisation number □□□□□□

Patient name: _____
Address: _____ _____
Post code:

The allocated drug class from the randomisation process is marked below:

SSRI Tricyclic Lofepamine

- You previously said that this class was **contraindicated**.
- We would like you to choose an appropriate medication either from those below or any other of your choice.
- Please tick the box below that corresponds with your choice.

<input type="checkbox"/> Fluoxetine	<input type="checkbox"/> Amitriptyline	<input type="checkbox"/> Lofepamine
<input type="checkbox"/> Paroxetine	<input type="checkbox"/> Dothiepin	
<input type="checkbox"/> Sertraline	<input type="checkbox"/> Imipramine	

If you have elected to prescribe another drug please state which
.....

Starting dose □□□ mg

Signed Date: □□-□□-□□

**Please return this form by faxing it back to the research team on:
(023) 8082 5538 or (023) 8023 4243.**

Appendix II

Self-report questionnaire for use of health and social service

Booklet no.

 1-4

Follow up no.

 5-6

Randomisation no.

 7-11

We would like to know whether you have had any contacts with the social services listed below and, if so, the number of times you have had contacts with them in the last month

Please check the diary sheet we gave you, and put '00' if you had no contact. Please put the number of times in the appropriate boxes

General practice and community nursing services

- | | | |
|---|---|-------------------------|
| Number of times you saw a GP at the surgery | <input type="text"/> <input type="text"/> | 12-13 |
| Number of times you saw a GP at your home | <input type="text"/> <input type="text"/> | 14-15 |
| Number of times you spoke to a GP on the telephone | <input type="text"/> <input type="text"/> | 16-17 |
| Number of times you saw a practice nurse at the surgery | <input type="text"/> <input type="text"/> | 18-19 |
| Number of times you saw a district nurse at your home | <input type="text"/> <input type="text"/> | 20-21 |
| Number of times you saw a counsellor at the surgery | <input type="text"/> <input type="text"/> | 22-23 |
| Number of contacts with anyone else from the practice | <input type="text"/> <input type="text"/> | 24-25 |
| Who did you see? | | <input type="text"/> 26 |
| Number of contacts with a health visitor | <input type="text"/> <input type="text"/> | 27-28 |

Social Services

- | | | |
|--|---|-------------------------|
| Number of times you saw a social worker | <input type="text"/> <input type="text"/> | 29-30 |
| Where did you see the social worker? | | <input type="text"/> 31 |
| Number of times you saw a home help | <input type="text"/> <input type="text"/> | 32-33 |
| Number of times you saw a care assistant | <input type="text"/> <input type="text"/> | 34-35 |
| Number of times you visited a Day Centre | <input type="text"/> <input type="text"/> | 36-37 |
| Number of contacts with anyone else from Social Services | <input type="text"/> <input type="text"/> | 38-39 |
| Who did you see? | | <input type="text"/> 40 |

Draft

Psychiatric Hospital and Community Services

Number of times you saw a psychiatrist at the hospital clinic	<input type="checkbox"/> <input type="checkbox"/>	41-42
Number of times you saw a psychiatrist at your home	<input type="checkbox"/> <input type="checkbox"/>	43-44
Number of times you saw a psychologist	<input type="checkbox"/> <input type="checkbox"/>	45-46
Number of times you saw a community psychiatric nurse	<input type="checkbox"/> <input type="checkbox"/>	47-48
Number of contacts with anyone else from the psychiatric services	<input type="checkbox"/> <input type="checkbox"/>	49-50
Who did you see?		<input type="checkbox"/> 51

Other Services

Number of times you attended a Day Hospital	<input type="checkbox"/> <input type="checkbox"/>	52-53
Number of times you went to the Accident and Emergency Department	<input type="checkbox"/> <input type="checkbox"/>	54-55
Number of times you went to a hospital clinic	<input type="checkbox"/> <input type="checkbox"/>	56-57
Number of nights you spent on a hospital ward	<input type="checkbox"/> <input type="checkbox"/>	58-59
Occupational or employment health services	<input type="checkbox"/> <input type="checkbox"/>	60-61
Number of contacts with anyone else from the hospital	<input type="checkbox"/> <input type="checkbox"/>	62-63
Please say who you saw		<input type="checkbox"/> 64

We are also interested in how many times each of the following may have happened to you, regardless of whether they led you to make contact with one of the types of services listed above. If any of the following has happened, please write the number of times in the appropriate box.

How many times during the past **FOUR weeks** did you have each of the following: accidents, injuries or other mishaps?

In the street or on the roads (for example, as a driver, cyclist or pedestrian)	<input type="checkbox"/> <input type="checkbox"/>	65-66
While at work	<input type="checkbox"/> <input type="checkbox"/>	67-68
In your home (e.g., a fall, a burn etc.)	<input type="checkbox"/> <input type="checkbox"/>	69-70
While taking your medication (i.e., took too many pills by mistake)	<input type="checkbox"/> <input type="checkbox"/>	71-72

Please give a brief description of things that happened which you have included above

73-74

Booklet no.

 75-78

Follow up no.

 79-80

Randomisation no.

 81-85

We know from experience that some people suffering from depression are tempted to take an overdose or otherwise try to harm themselves. We hope that this does not apply to you, but if it does we are keen to know about it. Of course this information will, as always, be treated in the strictest confidence.

Please do not count accidents covered under the previous question

Have you taken an overdose in the past **FOUR weeks**? Yes No times
 If yes, please write the number of times in the boxes

86/1/2
87-88

Have you done anything else to try to harm yourself in the past **FOUR weeks**? If yes, please write the number of times in the boxes Yes No times

89/1/2
90-91

On how many days during the past FOUR weeks were you unable to carry out your normal daily activities (e.g., housework, hobbies, go to work) because of ill health? days

92-93

Please could you write today's date in the boxes:
 Day Month Year
--

94-101

Interview/post Interview Post
 1 2

102/1/2

Interviewer JM JC AT Other
 1 2 3 4

103/1/2/3/4

One month/3 month questionnaire 1 month 3 month
 1 2

104/1/2

Draft

Appendix 12

Tables relating to SF-36 and EQ-5D data

SF-36 scores

TABLE 64 SF-36 scores on the role limitation due to emotional problems dimension

		SF-36 role limitation due to emotional problems scores																			
		TCA					SSRI					LOF					All				
		0	3	6	9	12	0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
(a) All patients																					
Mean	24.3	61.3	69.6	68.6	78.2	21.1	55.9	57.2	74.4	75.3	24.4	51.7	70.0	69.9	71.7	23.3	56.4	65.3	71.1	75.3	
SD	31.9	43.2	41.4	42.0	35.1	30.6	42.1	45.6	38.1	39.0	33.1	41.0	39.4	43.3	42.7	31.8	42.1	42.6	40.8	38.6	
IQR (lower)	0	0	33	33	67	0	0	0	33	67	0	0	33	33	33	0	0	33	33	33	
IQR (upper)	33	100	100	100	100	33	100	100	100	100	33	100	100	100	100	33	100	100	100	100	
n	107	75	57	52	58	106	74	60	56	54	105	69	50	41	46	318	218	167	149	158	
(b) Acceptors only																					
Mean	21.9	59.3	74.3	69.5	79.5	21.3	56.8	58.8	75.4	73.9	24.2	52.9	68.4	69.9	74.0	22.5	56.3	66.1	72.0	75.8	
SD	30.4	44.9	38.8	42.3	35.6	31.9	43.5	45.5	38.1	39.7	33.2	40.1	39.5	44.2	41.2	31.8	42.7	42.1	40.9	38.6	
IQR (lower)	0	0	67	33	67	0	0	0	67	33	0	0	33	0	33	0	0	33	33	33	
IQR (upper)	33	100	100	100	100	33	100	100	100	100	33	100	100	100	100	33	100	100	100	100	
n	61	45	35	35	39	89	64	51	46	46	77	51	38	31	32	227	160	124	112	117	

TABLE 65 SF-36 scores on the general health perception dimension

		SF-36 general health perception scores																			
		TCA					SSRI					LOF					All				
		0	3	6	9	12	0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
(a) All patients																					
Mean	56.8	65.8	65.0	67.7	67.7	52.7	59.9	65.6	64.5	66.6	53.0	57.4	65.9	67.6	61.1	54.2	61.2	65.5	66.5	65.3	
SD	22.8	21.2	23.0	21.3	22.2	21.8	22.3	19.6	23.7	23.6	22.5	25.1	22.9	23.0	25.3	22.4	23.0	21.7	22.6	23.7	
IQR (lower)	42	55	52	52	52	35	37	52	45	50	35	35	55	52	40	35	42	52	50	47	
IQR (upper)	72	82	82	87	82	67	77	82	85	87	72	77	82	82	82	72	82	82	87	82	
n	111	77	57	52	55	104	73	59	56	55	104	68	52	42	47	319	218	168	150	157	
(b) Acceptors only																					
Mean	57.9	66.6	70.2	69.2	70.2	53.5	59.6	65.9	65.8	67.1	53.5	55.9	65.3	66.2	61.1	54.8	60.5	66.9	67.0	66.4	
SD	21.7	20.7	18.9	18.8	21.3	21.5	21.2	18.6	21.9	22.8	21.8	24.8	22.5	23.0	23.5	21.6	22.5	19.9	21.1	22.6	
IQR (lower)	42	54	55	52	52	37	37	52	45	50	35	32	57	52	42	37	42	55	52	50	
IQR (upper)	72	82	82	87	82	67	77	82	82	87	67	77	82	82	80	70	77	82	85	82	
n	66	48	35	35	38	87	63	50	46	47	76	51	39	31	33	229	162	124	112	118	

EQ-5D scores

TABLE 66 EQ-5D thermometer scale (including interpolated scores)

Month:	EQ-5D thermometer scale (including interpolated scores)																				
	TCA						SSRI						LOF								
	0	1	2	3	6	9	12	0	1	2	3	6	9	12	0	1	2	3	6	9	12
(a) All patients																					
Mean	53.4	62.8	69.2	72.0	74.4	76.4	77.9	53.6	63.4	68.0	68.0	73.6	74.2	76.6	49.0	54.3	60.6	66.5	71.8	71.9	68.9
SD	19.8	18.9	17.6	17.1	18.6	17.9	17.7	19.6	18.5	19.5	21.0	17.6	19.3	17.5	17.0	18.1	19.8	19.6	18.6	21.7	24.2
IQR (lower)	40	50	55	60	60	60	70	40	50	50	50	60	63	65	40	45	50	50	50	51	50
IQR (upper)	70	75	81	85	89	90	90	70	80	83	85	90	90	90	60	62	71	80	90	90	90
n	111	93	87	83	67	63	59	106	86	82	78	70	62	58	104	83	80	78	62	60	50
(b) Acceptors only																					
Mean	53.6	61.4	68.9	71.7	76.3	77.6	78.9	53.4	62.5	67.8	67.8	74.2	74.7	76.8	48.3	53.5	59.6	65.4	71.3	71.4	67.4
SD	19.6	20.1	16.8	17.0	16.7	18.1	19.2	19.7	18.8	19.8	21.1	16.5	17.8	16.4	17.6	17.9	19.7	19.8	18.2	21.3	23.7
IQR (lower)	40	50	57	60	70	65	70	40	50	50	50	60	61	65	40	45	50	50	50	50	50
IQR (upper)	70	70	80	85	90	93	92	70	79	85	85	90	90	90	60	62	71	80	88	90	90
n	65	56	52	50	41	41	39	90	74	71	67	60	52	50	76	62	59	57	45	43	35

Appendix 13

Summary of unadjusted and adjusted EQ-5D scores and summary of resource use and costs from baseline to last EQ-5D

Summary of unadjusted EQ-5D tariff scores

The box plots in Figures 34–41 represent the distribution of the EQ-5D tariff scores

Key to boxplots:

- Lines represent median value.
- Boxes represent interquartile ranges.
- The tails represent the boundaries or 'fence' marking the lowest or highest observation that is not an outlier.
- Circles represent outliers (between 1.5 and 3 box lengths away from the 25th or 75th percentiles).
- Asterisks represent extremes (greater than 3 box lengths away from the 25th or 75th percentiles).

TABLE 67 Summary of unadjusted reported EQ-5D tariff scores for patients included in the cost–utility analysis

	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
TCA							
<i>n</i>	93	75	58	76	58	53	58
Mean	0.577	0.715	0.779	0.763	0.766	0.792	0.809
SD	0.271	0.225	0.234	0.249	0.253	0.241	0.213
SSRI							
<i>n</i>	85	67	57	71	62	56	56
Mean	0.608	0.726	0.775	0.732	0.741	0.790	0.819
SD	0.282	0.218	0.229	0.252	0.274	0.242	0.200
LOF							
<i>n</i>	83	59	57	71	52	44	48
Mean	0.574	0.674	0.753	0.742	0.763	0.794	0.700
SD	0.273	0.301	0.257	0.215	0.229	0.187	0.309
All patients							
<i>n</i>	261	201	172	218	172	153	162
Mean	0.586	0.707	0.769	0.746	0.756	0.792	0.780
SD	0.275	0.247	0.239	0.239	0.253	0.226	0.246

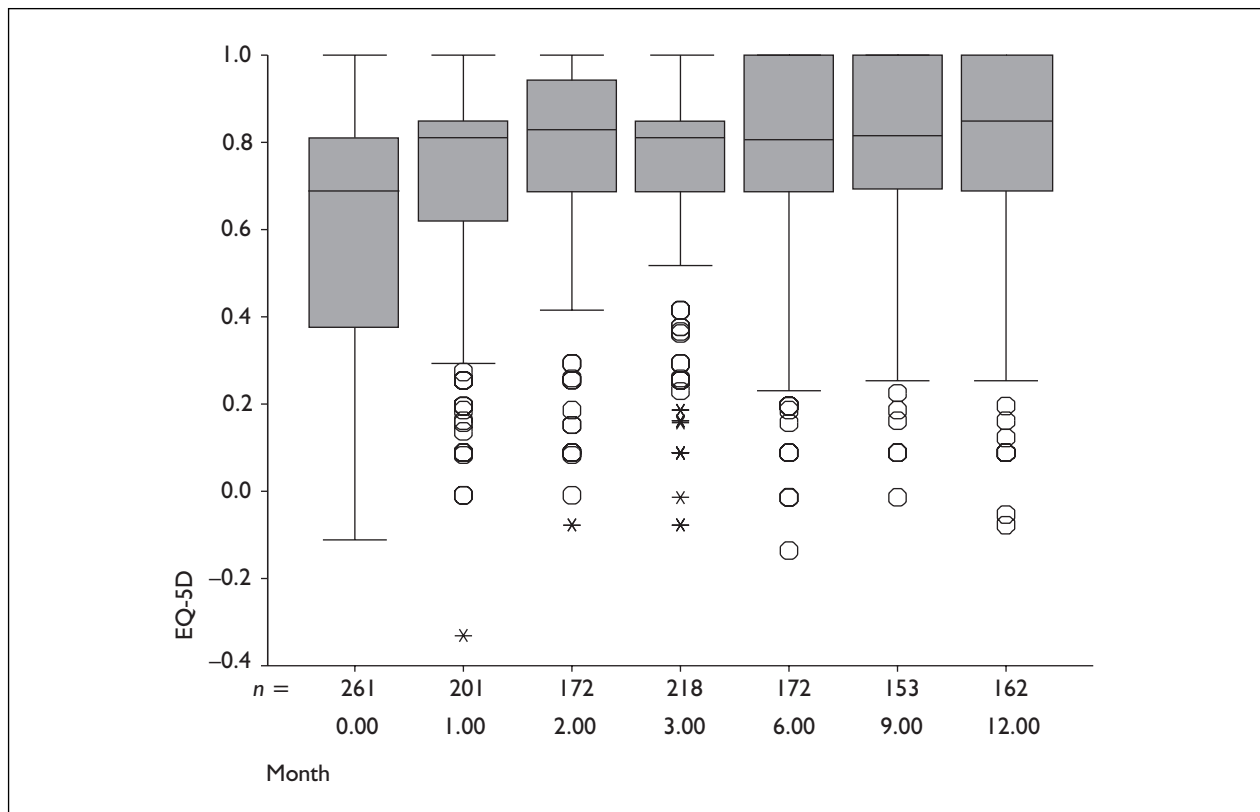


FIGURE 34 Boxplot of reported EQ-5D tariff scores for all patients included in the cost-utility analysis

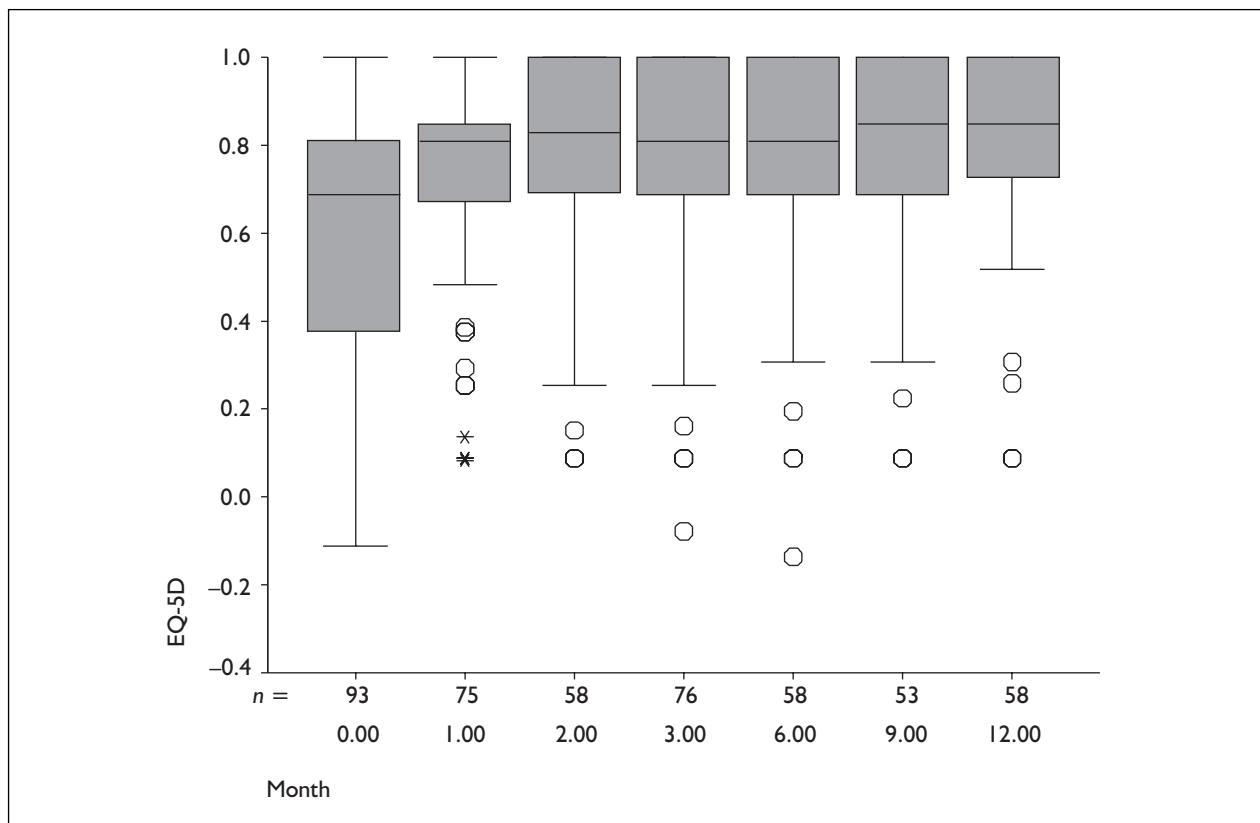


FIGURE 35 Boxplot of reported EQ-5D tariff scores for patients randomised to TCAs

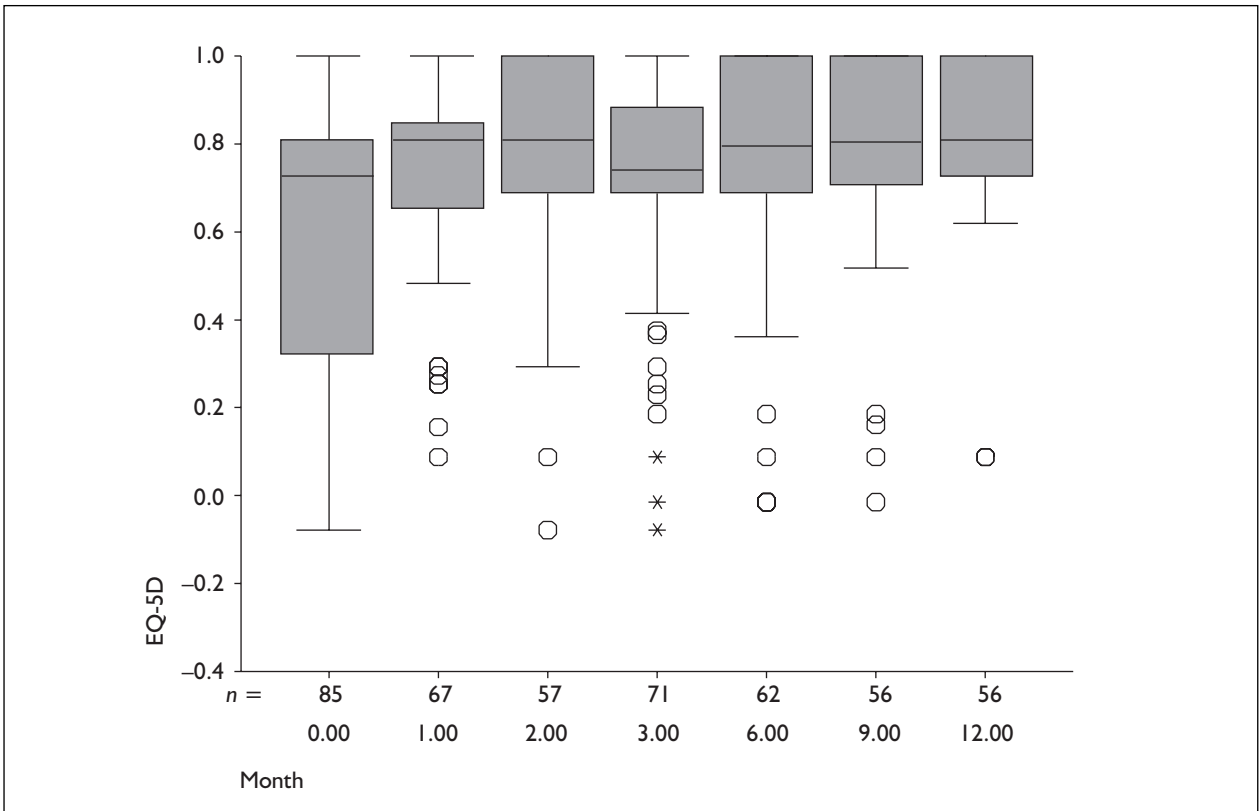


FIGURE 36 Boxplot of reported EQ-5D tariff scores for patients randomised to SSRIs

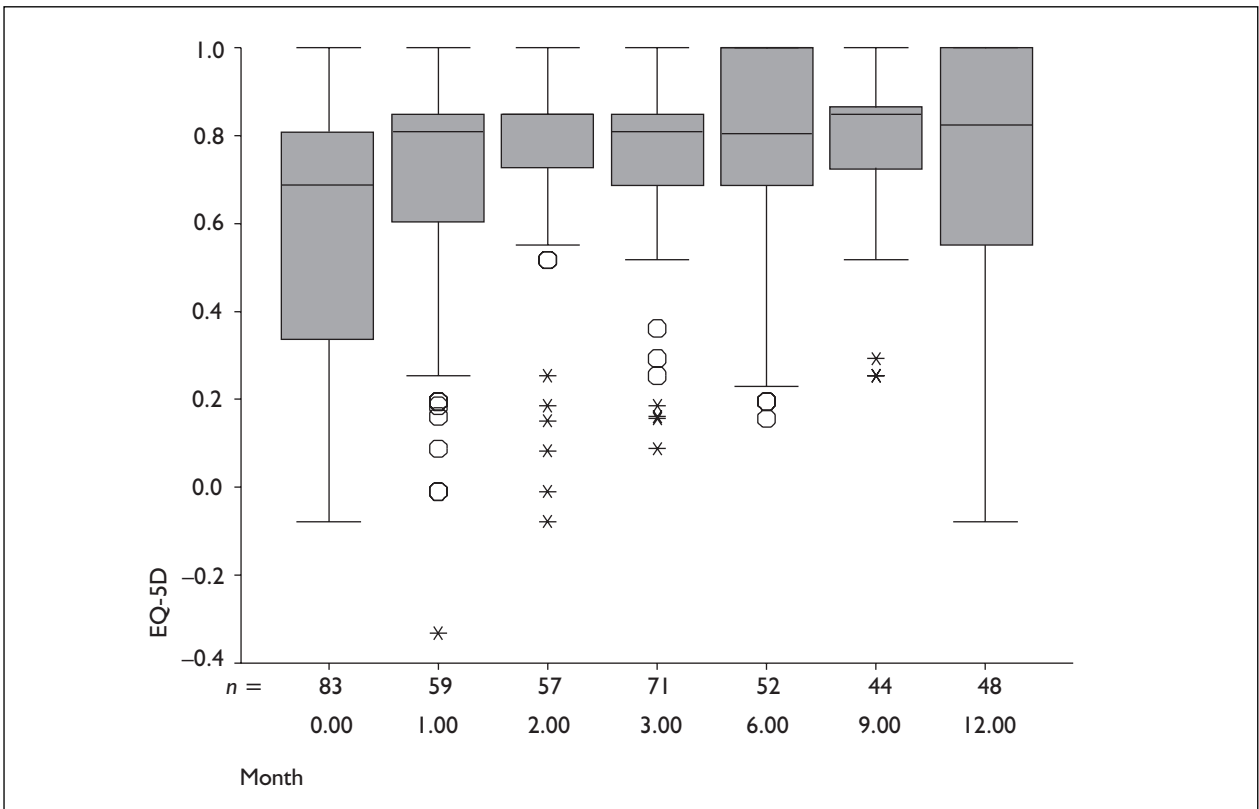


FIGURE 37 Boxplot of reported EQ-5D tariff scores for patients randomised to LOF

Summary of adjusted EQ-5D tariff scores

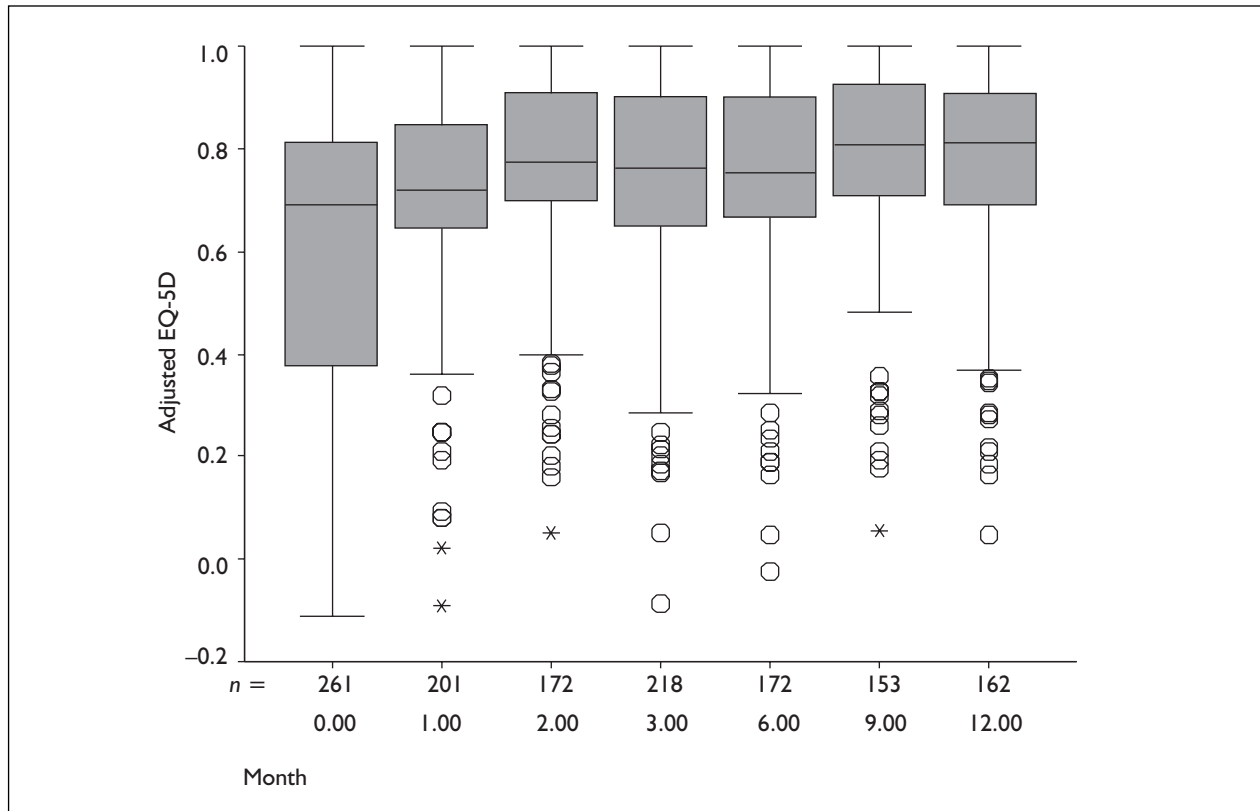


FIGURE 38 Boxplot of EQ-5D tariff scores for all patients adjusted for baseline differences

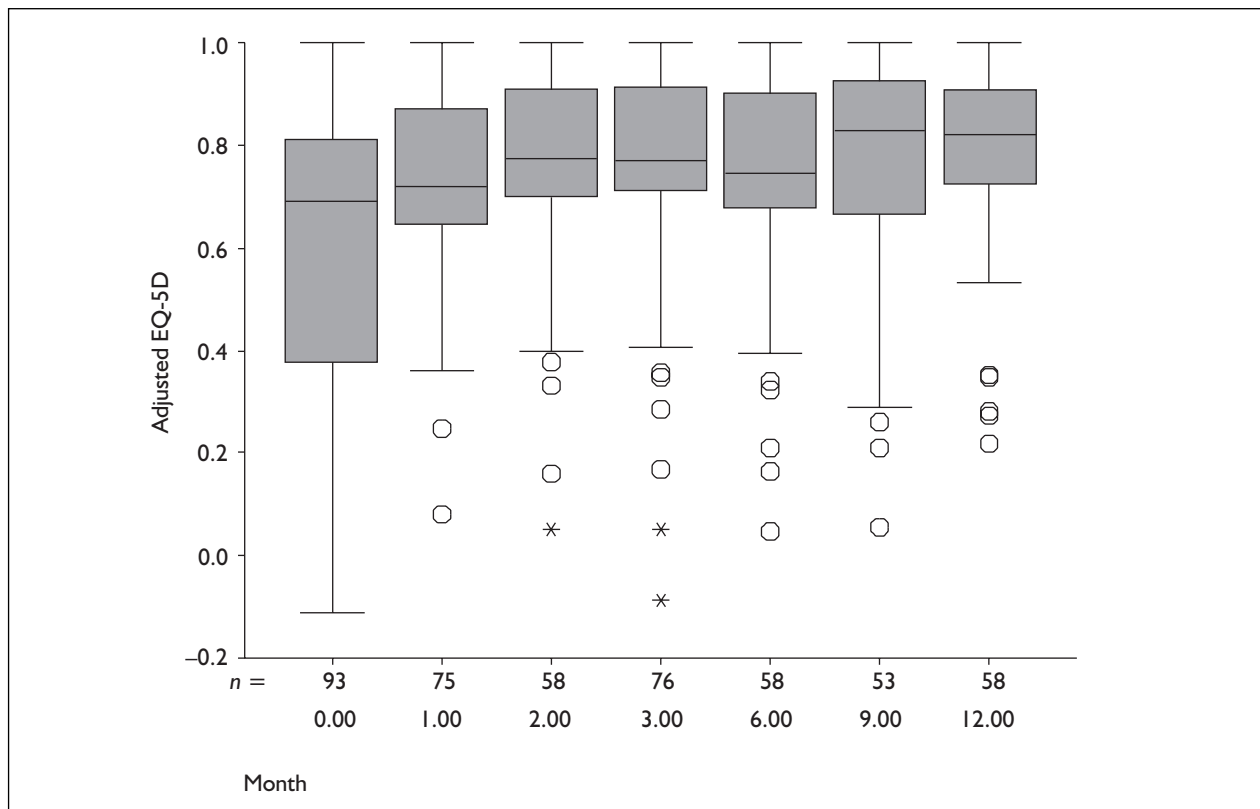


FIGURE 39 Boxplot of EQ-5D tariff scores for patients randomised to TCAs adjusted for baseline differences

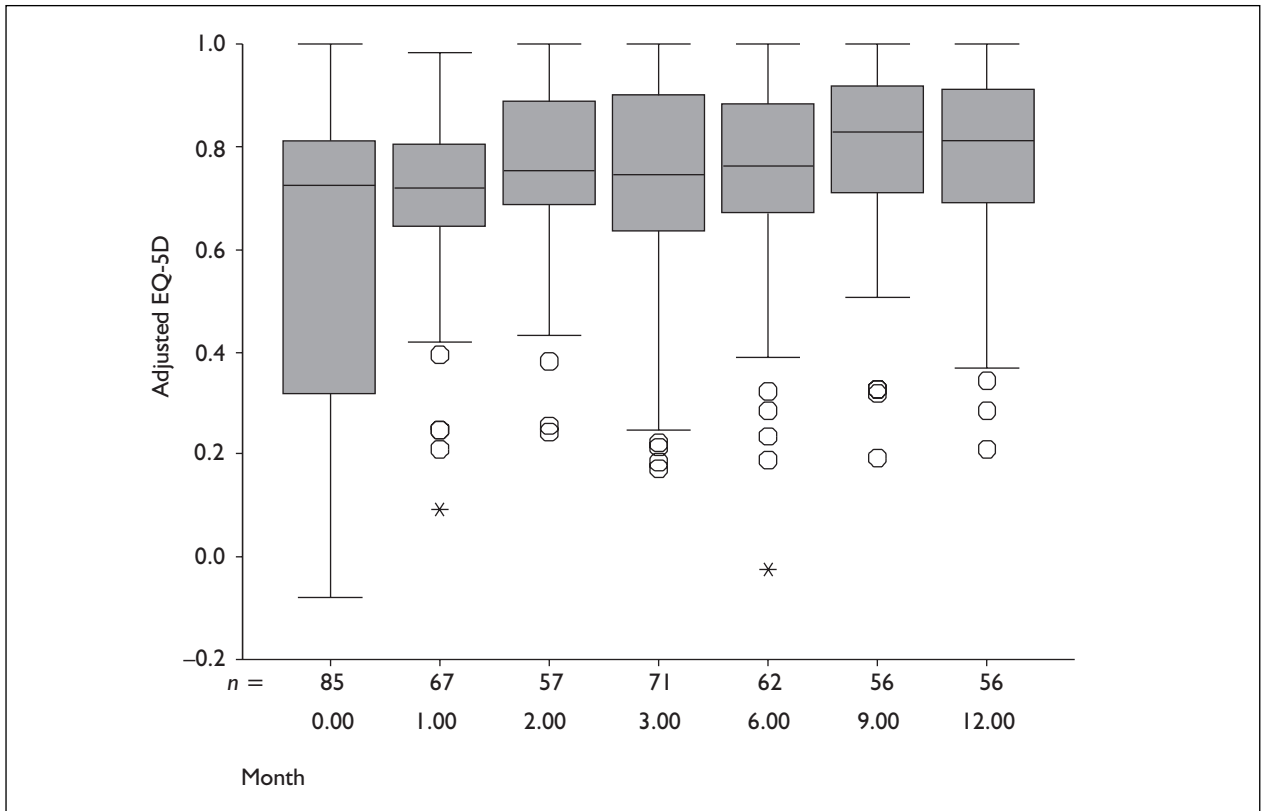


FIGURE 40 Boxplot of EQ-5D tariff scores for patients randomised to SSRIs adjusted for baseline differences

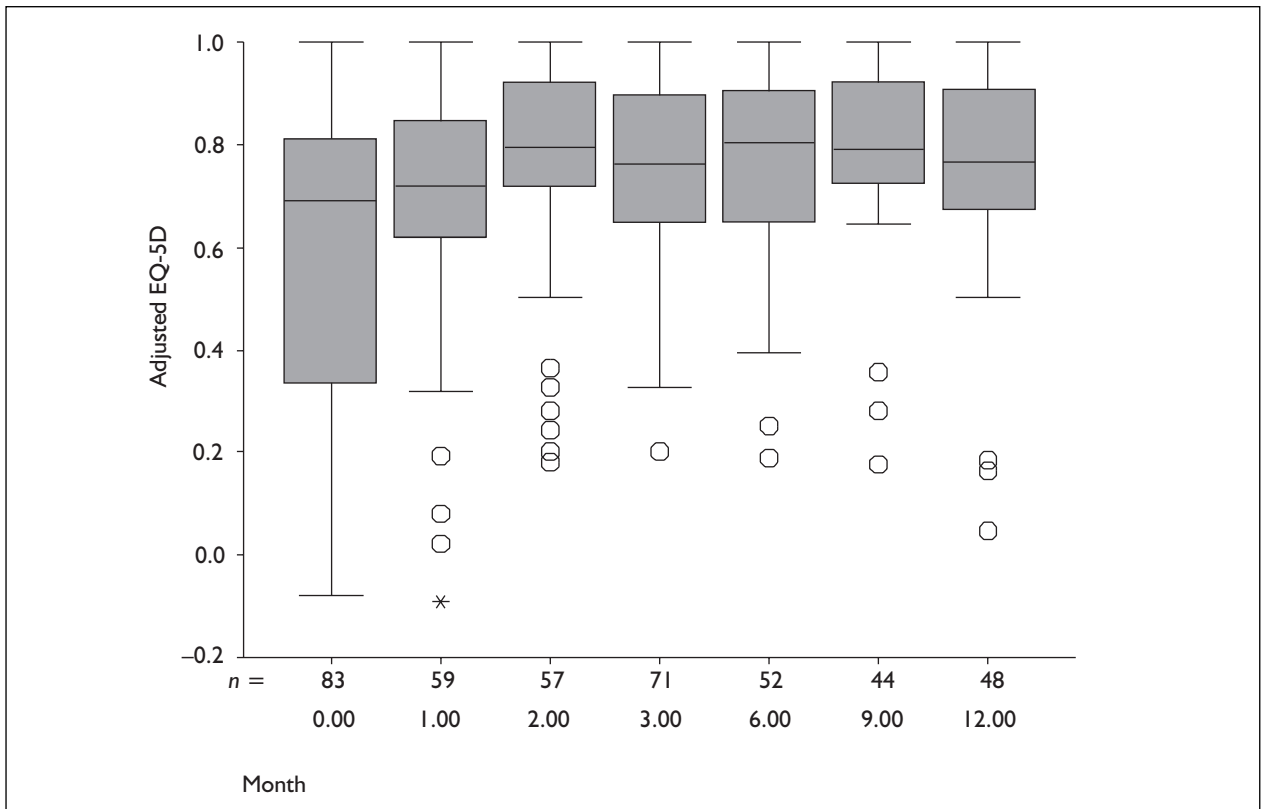


FIGURE 41 Boxplot of EQ-5D tariff scores for patients randomised to LOF adjusted for baseline differences

Summary of resource use and costs from baseline to last EQ-5D

TABLE 68 Details of inpatient stay from randomisation to date of last EQ-5D

	TCA (n = 93)	SSRI (n = 85)	LOF (n = 83)	All (n = 261)
Psychiatric inpatient stay only (days), mean (SD)	0.66 (5.07)	0 (0)	0.11 (1.00)	0.27 (3.10)
All inpatient stay (days), mean (SD)	1.38 (5.93)	0.65 (3.03)	0.49 (1.60)	0.86 (4.05)

TABLE 69 Mean (SD) number of contacts for other key items of non-drug resource-use stay from randomisation to date of last EQ-5D

	TCA (n = 93)	SSRI (n = 85)	LOF (n = 83)	All (n = 261)
Visit to GP at surgery	7.13 (4.67)	8.41 (6.73)	7.82 (5.56)	7.77 (5.69)
Contact with GP by telephone	0.69 (1.98)	1.29 (3.29)	0.48 (1.07)	0.82 (2.32)
Home visit by GP	0.20 (0.70)	0.41 (1.52)	0.25 (0.76)	0.29 (1.06)
Contact with practice nurse at surgery	0.89 (1.35)	1.54 (2.69)	1.11 (1.91)	1.17 (2.05)
Home visit by district nurse	0.90 (7.50)	0.42 (2.59)	0.05 (0.35)	0.48 (4.71)
Contact with community psychiatric nurse	0.03 (0.18)	0.06 (0.32)	0.31 (1.82)	0.13 (1.05)
Visit to counsellor	0.23 (0.82)	0.51 (1.69)	0.40 (1.31)	0.37 (1.31)
Attendance at day centre	0.54 (3.72)	0 (0)	0.53 (3.81)	0.36 (3.09)
Attendance at non-psychiatric clinic	0.72 (1.57)	1.07 (2.30)	0.77 (1.51)	0.85 (1.82)
Contact with psychiatrist	0.11 (0.67)	0.02 (0.15)	0.16 (0.57)	0.10 (0.52)
Visit to A&E	0.11 (0.45)	0.25 (0.65)	0.13 (0.34)	0.16 (0.50)

TABLE 70 Results of the Kruskal–Wallis test for differences in resource use between the three groups

	χ^2 (2 df)	p
Visit to GP at surgery	2.32	0.313
Contact with GP by telephone	3.52	0.173
Home visit by GP	0.15	0.929
Contact with practice nurse at surgery	1.39	0.500
Home visit by district nurse	0.05	0.978
Contact with community psychiatric nurse	0.10	0.954
Visit to counsellor	0.54	0.764
Attendance at day centre	0.14	0.934
Attendance at non-psychiatric clinic	0.49	0.785
Contact with psychiatrist	0.69	0.711
Visit to A&E	1.29	0.526



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We look forward to hearing from you.