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A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 97/29/01. The contractual start date was in September 2000. The draft report began editorial review in March 2006 and was accepted for publication in October 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial

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Objectives: To determine if, in the short term, depressed adolescents attending routine NHS Child and Adolescent Mental Health Services (CAMHS), and receiving ongoing active clinical care, treatment with selective serotonin reuptake inhibitors (SSRIs) plus cognitive behaviour therapy (CBT) compared with SSRI alone, results in better healthcare outcomes.

Design: A pragmatic randomised controlled trial (RCT) was conducted on depressed adolescents attending CAMHS who had not responded to a psychosocial brief initial intervention (BII) prior to randomisation.

Setting: Six English CAMHS participated in the study.

Participants: A total of 208 patients aged between 11 and 17 years were recruited and randomised.

Interventions: All participants received active routine clinical care in a CAMHS outpatient setting and an SSRI and half were offered CBT.

Main outcome measures: The duration of the trial was a 12-week treatment phase, followed by a 16-week maintenance phase. Follow-up assessments were at 6, 12 and 28 weeks. The primary outcome measure was the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA). Secondary outcome measures were self-report depressive symptoms, interviewer-rated depressive signs and symptoms, interviewer-rated psychosocial impairment and clinical global impression of response to treatment. Information on resource use was collected in interview at baseline and at the 12- and 28-week follow-up assessments using the Child and Adolescent Service Use Schedule (CA-SUS).

Results: Of the 208 patients randomised, 200 (96%) completed the trial to the primary end-point at 12 weeks. By the 28-week follow-up, 174 (84%) participants were re-evaluated. Overall, 193 (93%) participants had been assessed at one or more time points. Clinical characteristics indicated that the trial was conducted on a severely depressed group. There was significant recovery at all time points in both arms. The findings demonstrated no difference in treatment effectiveness for SSRI + CBT over SSRI only for the primary or secondary outcome measures at any time point. This lack of difference held when baseline and treatment characteristics where taken into account (age, sex, severity, co-morbid characteristics, quality and quantity of CBT treatment, number of clinic attendances). The SSRI + CBT group was somewhat more expensive over the 28 weeks than the SSRI-only group ($p = 0.057$) and no more cost-effective. Over the trial period there was on average a decrease in suicidal thoughts and self-harm compared with levels recorded at baseline. There was no significant increase in disinhibition, irritability and violence compared with levels at baseline. Around 20% ($n = 40$) of patients in the trial were non-responders. Of these, 17 (43%) showed no improvement by 28 weeks and 23 (57%) were considered minimally ($n = 10$) or moderately to severely worse ($n = 13$).

Conclusions: For moderately to severely depressed adolescents who are non-responsive to a BII, the addition of CBT to fluoxetine plus routine clinical care does not improve outcome or confer protective effects against adverse events and is not cost-effective. SSRIs (mostly fluoxetine) are not likely to result in harmful adverse effects. The findings are broadly consistent with existing guidelines on the treatment of moderate

to severe depression. Modification is advised for those presenting with moderate (6–8 symptoms) to severe depressions (>8 symptoms) and in those with either overt suicidal risk and/or high levels of personal impairment. In such cases, the time allowed for response to psychosocial interventions should be no more than 2–4 weeks, after which fluoxetine should be prescribed. Further research should focus on evaluating the efficacy of specific psychological treatments against brief psychological intervention, determining the characteristics of patients with severe depression who are non-responsive to fluoxetine, relapse prevention in severe depression and improving tools for determining treatment responders and non-responders.

Contents

List of abbreviations

ACC	active clinical care
ADAPT	Adolescent Depression Antidepressant and Psychotherapy Trial
BII	brief initial intervention
CAMHS	Child and Adolescent Mental Health Services
CA-SUS	Child and Adolescent Service Use Schedule
CBT	cognitive behaviour therapy
CDRS-R	Revised Children's Depression Rating Scale
CEAC	cost-effectiveness acceptability curve
CGAS	Children's Global Assessment Scale
CGI	clinical global improvement
CI	confidence interval
DNA	did not attend
GHQ-28	General Health Questionnaire
HoNOSCA	Health of the Nation Outcome Scales for Children and Adolescents
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPT	interpersonal psychotherapy
ITCC	intra-therapist correlation coefficient
ITT	intention-to-treat
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version
MDD	major depressive disorder
MFQ	Mood and Feelings Questionnaire
NICE	National Institute for Health and Clinical Excellence
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SD	standard deviation
SSRI	selective serotonin reuptake inhibitor
TADS	Treatment for Adolescents with Depression Study

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

Background

Unipolar depression in adolescents is a serious mental disorder with a high rate of recurrence and relapse into adult life. Interventions to treat the disorder, improve adult outcomes and diminish subsequent healthcare costs are much needed. To date there have been no randomised control trials (RCTs) of selective serotonin reuptake inhibitors (SSRIs) carried out on moderate to severely depressed adolescents attending NHS facilities.

Objectives

The aim of this study was to determine if, in the short term, depressed adolescents attending routine NHS Child and Adolescent Mental Health Services (CAMHS), and receiving ongoing active clinical care, treatment with SSRIs plus cognitive behaviour therapy (CBT) compared with SSRI alone, results in better healthcare outcomes. The specific research hypotheses addressed were that compared with SSRIs alone, combined treatment would over the length of the trial:

- result in greater psychosocial improvement
- diminish the overall level of depressive symptoms
- result in fewer patients meeting diagnostic criteria at final evaluation
- decrease other public service use and be more cost-effective.

In order to achieve these objectives, an RCT of adolescent patients fulfilling criteria for DSM-IV major depression or with threshold major depression (four symptoms) and marked impairment was undertaken.

Design

A pragmatic RCT was conducted on depressed adolescents attending CAMHS who had not responded to a psychosocial brief initial intervention (BII) prior to randomisation.

Setting

Participants were recruited from two centres, Manchester in the north-west and Cambridge in the east of England. Six CAMHS participated: four in Manchester (total population 831,000) and two in Cambridge (total population 517,000).

Participants

A total of 208 patients aged between 11 and 17 years were recruited and randomised.

Interventions

All participants received active routine clinical care in a CAMHS outpatient setting and an SSRI and half were offered CBT.

Outcome measures

The duration of the trial was a 12-week treatment phase, followed by a 16-week maintenance phase. Follow-up assessments were at 6, 12 and 28 weeks. The primary outcome measure was the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA). Secondary outcome measures were self-report depressive symptoms, interviewer-rated depressive signs and symptoms, interviewer-rated psychosocial impairment and clinical global impression of response to treatment. Information on resource use was collected in interview at baseline and at the 12- and 28-week follow-up assessments using the Child and Adolescent Service Use Schedule (CA-SUS).

Results

Of the 208 patients randomised, 200 (96%) completed the trial to the primary end-point at 12 weeks. By the 28-week follow-up, 174 (84%) participants were re-evaluated. Overall, 193 (93%) participants had been assessed at one or more

time points. Clinical characteristics indicated that the trial was conducted on moderate to severely depressed group. There was significant recovery at all time points in both arms. The findings demonstrated no difference in treatment effectiveness for SSRI + CBT over SSRI only for the primary or secondary outcome measures at any time point. This lack of difference held when baseline and treatment characteristics where taken into account (age, sex, severity, co-morbid characteristics, quality and quantity of CBT treatment, number of clinic attendances). The SSRI + CBT group was somewhat more expensive over the 28 weeks than the SSRI-only group ($p = 0.057$) and no more cost-effective. Over the trial period there was on average a decrease in suicidal thoughts and self-harm compared with levels recorded at baseline. There was no significant increase in disinhibition, irritability and violence compared with levels at baseline. Around 20% ($n = 40$) of patients in the trial were non-responders. Of these, 17 (43%) showed no improvement by 28 weeks and 23 (57%) were considered minimally ($n = 10$) or moderately to severely worse ($n = 13$).

Conclusions

For moderately to severely depressed adolescents who are non-responsive to a BII, the addition of CBT to fluoxetine plus routine clinical care in moderate to severe depressions does not improve outcome or confer protective effects against adverse events and is not cost-effective. SSRIs (mostly fluoxetine) are not likely to result in harmful adverse effects.

The findings are broadly consistent with the National Institute for Health and Clinical Excellence guidelines on the treatment of moderate to severe depression. Modification is advised for those presenting with moderate (6–8 symptoms) to severe (>8 symptoms) depressions and in those with either overt suicidal risk and/or high levels of personal impairment. In such cases, the time allowed for response to psychosocial interventions should be no more than 2–4 weeks, after which fluoxetine should be prescribed.

Recommendations for future research

Further research is recommended in the following areas:

- **Evaluate the efficacy of specific psychological treatments against brief psychological intervention**. The current findings provide anecdotal information for the putative effectiveness of BII for some cases of depression. BII can most likely be delivered by all routine CAMHS services. It is not clear if BII would be as safe and effective as CBT, family or interpersonal psychotherapy (IPT), for adolescents with moderate depressions.
- **Determine the characteristics of patients with severe depression who are non-responsive to fluoxetine**. It is likely that non-responders will be heavy healthcare users into adult life. Delineating their characteristics and their pattern of healthcare use, including compliance with treatment offered as adolescents, would be a key study.
- **A study into relapse prevention in severe depressions**. Preventing relapse will reduce the risks associated with multiple depressive episodes. Candidate models include assertive outreach, dealing with non-health barriers to rehabilitation (education, skills development and work entry); CBT or IPT in healthcare settings; family therapies to reduce negative environments in the home; and befriending techniques to re-engage adolescent peer group often lost during a depressive episode. Relapse prevention may improve outcome into adult life and diminish healthcare cost in the medium term. A longer term study with follow up for 2 years post-remission is required to address these questions.
- **Improve the tools for determining treatment responders and non-responders**. A weakness in all trials to date, including this study, is the precision of measurement to assess both the nature of the disorder and treatment response. New tools are urgently required. These should go beyond surface aspects of the clinical phenotype. Such research must also determine the most efficient delivery mode to the clinic of any new and valid test procedure and its cost benefits to the service.

Chapter 1
Introduction

Unipolar depression in young people

Unipolar major depression is a serious mental disorder which often emerges in the first two decades of life.[1] The condition is rare in prepubertal children but increasingly common by mid-adolescence (13–16 years).[1] Between 13 and 18 years of age, the 12-month prevalence for a first episode of unipolar major depressive disorder (MDD) is approximately 3% of females and 1% of males.[1] In the UK primary and secondary school age population excluding sixth formers (i.e. those aged 5–16 years), around 80% of all first episodes occur after 13 and before 17 years.[2,3] Furthermore, there are time trends that point to increased rates of depressive disorders, rising since the mid-twentieth century with first episodes occurring at an earlier age.[4–7] Current estimates suggest that overall some 13–20% of adolescents will experience an episode of depression of some form and severity before they reach their third decade.

These first episode disorders in the adolescent years are associated with a high risk of recurrence and relapse into adult life.[8] In the adult years, those with a history of depression in adolescence have higher rates of personality disorder, substance misuse and suicidal behaviour.[9,10] Finally, there is recent evidence that a small but significant proportion of adolescents with MDD remain persistently depressed through into their early twenties.[11]

Although first episodes arise in the main in vulnerable individuals exposed to chronic psychosocial adversities,[12–14] recurrent disorder is associated with markedly fewer external stressors suggesting alterations in brain function over time as a consequence of depressive illness.[15,16] Thus depressive episodes may themselves increase the risk for further illness regardless of the level of adversities in the social environment. Recent epidemiological findings have noted that constitutional factors are likely to account for a significant proportion of risk for psychopathology in young people.[17] Finally, the liability for the development of brain vulnerabilities secondary to depressive episodes may depend in part on the length of an established depressive episode.[11]

Hence the adverse outcomes associated with adolescent MDD indicate the importance of detecting individuals in episode early and delivering effective treatments as rapidly as possible, both to accelerate time to recovery and to diminish the length of episode.

From a policy perspective, it is also important to consider the extent to which effective treatments are deliverable and affordable. Few, if any, treatment studies in child mental health have given consideration to the health economic implications of implementing treatment. There is increasing evidence for an economic burden accrued from individuals with a history of depression in the school age years through high service use in adulthood.[18] There is also evidence that adolescents who develop MDD have higher than expected use of mental health services in the years prior to the overt clinical emergence of their disorder. Data from the UK child mental health survey have shown that nearly three-quarters (73%) of the parents of children with an emotional disorder had sought some form of advice or help because of concerns about the child's mental health. Just under two-thirds (64%) had contacted a professional source, usually a teacher (47%).[3] It is increasingly apparent that assessing the economic value of treatments delivered to depressed adolescents will provide an important dimension for healthcare policy makers and planners. A key component of treatment and service research is therefore to include cost measures in research design and assessment of cost-effectiveness.

Are there effective treatments for depressed adolescents?

Treatment studies of depressed youth have been slowly emerging since the mid-1980s. In the first decade both psychosocial and psychotropic agents were used and reported as showing moderate effects in clinical populations. Reviews of these early studies were encouraging but noted considerable deficiencies in methods and procedures.[19] By 1997, the number of published studies had advanced somewhat but there remained serious concerns as to the quality of the

majority. In particular, the absence of a randomised control trial (RCT) design with sufficient sample size comparing potentially effective treatments against each other was notably missing from the existing literature. By the mid- to late-1990s, there were two treatments with growing validity being delivered in Child and Adolescent Mental Health Services (CAMHS) services worldwide, including the UK, namely cognitive behaviour therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs). By 1998, treatment reviews and meta-analyses had concluded that CBT was the treatment of choice for children and adolescents with clinical depression.[20–22] Harrington and colleagues noted, however, that there had been no systematic treatment studies comparing psychological treatments with medication.[20] The American Academy of Child and Adolescent Psychiatry published practice parameters in 1998 which broadly concurred with Harrington and colleagues' concerns but noted that since both psychotherapy and pharmacotherapy (mostly SSRIs) have been found to be beneficial independently of each other, it was difficult to formulate evidence-based procedures for treatment.[23] There were sufficient evidence and reviews from open and double-blind studies to state that SSRIs and fluoxetine in particular were potentially therapeutic.[24–26]

At the time of application for the current study (1998), there was a clear rationale for comparing two treatments in depressed youth, CBT and SSRIs. Further, there was evidence that depressive disorders were likely to benefit from treatment compared with no treatment. Thus an effectiveness trial with a no treatment group was not warranted and may be considered unethical. What was less clear was the best design for a study comparing putatively effective treatments that would achieve the most effective value for money and be deliverable to the NHS.

Rationale for the current trial design

The principal investigators of the current trial undertook a survey of best practice amongst consultant child and adolescent psychiatrists in the North West and East Anglian Regions of the UK in the calendar year 1998. Participants were asked to identify their treatment of choice and mode of delivery of this treatment to adolescents referred to outpatient services and who met criteria (DSM IV or ICD 10) for MDD. Of the 50 consultants surveyed, 45 (90%) responded and there was nearly unanimous opinion that SSRIs + CBT would be the treatment of choice once diagnosis had been established and supportive psychosocial treatments had effected no change over the first month of treatment. The latter were likely to include explanation of diagnosis and natural history of depression and attention to any recent psychosocial adversities in the life of the child and/or family. All consultants who responded indicated that they would use a holistic approach to overall management. This included the involvement of parents and/or guardians at all stages of the treatment, examining the role of peer group and school environments in the onset and maintenance of disorder and treating and managing presenting complaints and non-depressive co-morbid conditions.

By the time of writing the proposal (1998), there were clear guidelines from statutory bodies including sufficient evidence from published work that generic treatment was significantly better than no treatment waiting list controls in the short term (6–12 weeks).[23] A placebo no treatment control arm was deemed unethical and a pragmatic trial was proposed comparing two active treatments. The choice of treatments was dictated by the focus on moderate to severe MDD cases attending routine outpatients within NHS CAMHS services. The principal applicants decided that the study population should reflect as closely as possible depressed patients seen in routine clinical CAMHS practice so that findings could be generalised to UK services as a whole.

The design should also take into account the fact that a proportion of individuals with MDD are likely to respond to general supportive psychosocial management as currently practised and described in the preliminary survey. Two key components of ascertainment were stressed in the proposal. The first was that depressed patients with suicidal ideation and/or acts, self-harm behaviours or severe psychosocial impairments that rendered them unable to participate in daily life would not be excluded. The majority of studies to date had excluded such patients on the grounds that they were either 'too ill' to participate or that the risks accrued to the researchers in randomising such participants to no treatment or weak effects treatments were too great and funding bodies would not accept indemnity for subsequent adverse outcomes. The second was that the research would take place on routine referrals and in standard treatment settings using NHS staff to deliver treatments under supervision such that ecological validity would be retained.

This was seen as a key factor in being able to deliver meaningful change to CAMHS services where resource allocation is likely to remain difficult for the foreseeable future. A strong evidence base is required to persuade primary care and mental health trusts, CAMHS managers and their clinical staff that a change in practice is not only desirable but doable within their local budgets.

Aims and objectives

The aim of this investigation was to compare two active treatments in routine outpatient CAMHS settings to inform clinical practice in the UK regarding the treatment of adolescents with MDD. Following the aforementioned clinical survey together with feedback from anonymous peer review, the original design was modified to take into account funding availability, time constraints to meet objectives and management of a large-scale RCT for this condition in this age range not previously undertaken. The first design had been to compare four active treatment arms (SSRIs alone, CBT alone, SSRIs + CBT combined, treatment as usual). The final design approved and funded was a comparison of SSRIs against SSRIs + CBT. We also decided that the trial would have greater validity if it randomised only cases that were unlikely to remit spontaneously in the 4 weeks after referral. Therefore, we applied a brief (2–4 sessions) general psychosocial intervention to all possible cases referred and entered into the trial only those who continued to meet criteria for major depression or probable major depression. Finally, the entry criteria were relaxed slightly to include sub-threshold depressions (equivalent to a DSM-IV minor episode) where patients presented with at least four depressive symptoms and significant psychosocial impairment. This change was deemed necessary by the applicants and the treatment team as evidence continues to accrue that these individuals have a significant depressive disorder whose natural history follows the same trajectory as those with major depression, which in effect is distinguished merely by the addition of one or more symptoms at entry.[27] Final diagnosis (major or minor) may therefore depend merely on fluctuation errors at the level of clinical measurement and exclusion of this group already referred was considered scientifically incorrect.

Primary objective

The primary objective of the trial was to determine in the short term if, in patients receiving ongoing active clinical care (ACC), combined treatment was more efficacious than single treatment in routine CAMHS settings. The study did not include an SSRI only or a CBT only arm without ACC and therefore cannot determine if either of these specialist treatments delivered by themselves is effective in the absence of ACC.

Specific hypotheses

In patients receiving ACC in routine NHS settings throughout the trial, SSRIs + CBT combined compared with SSRIs only would over the length of the trial:

- result in greater psychosocial improvement as the primary outcome
- diminish the overall level of depressive symptoms
- result in fewer patients meeting diagnostic criteria at final evaluation
- decrease the use of other health and social services and be more cost-effective.

In order to achieve these aims, an RCT of adolescent patients fulfilling criteria for DSM IV major depression together with a small number with sub-threshold disorder and attending CAMHS outpatient services through routine referral procedures was undertaken.

Chapter 2
Methods

Procedure

The procedure for the study was to ascertain and recruit patients with depression from routine clinical services in two parts of the UK, Manchester and Cambridge. Power calculations had determined that 200 patients would need to be recruited and randomised. The study team were funded to provide CBT and to undertake evaluations of treatment by two interviewers, one at each site, blind to randomisation. The healthcare trusts provided service support costs so that both centres had a full-time adolescent psychiatrist at specialist registrar level who was responsible for the coordination of outpatient care and specifically responsible for delivering SSRI treatment. All patients randomised received an SSRI. All the psychiatrists were trained in CBT and delivered this treatment together with other certified CBT therapists in the locality services. The psychiatrists consisted of two specialist registrars (PW, AL), one consultant-level psychiatrist (BD), and one professor (RCH). The professor was a well-known expert in CBT and supervisor and had co-written the manual. The consultant-level psychiatrist had received CBT training and experience with both adult and adolescent patients prior to doing the 3-day course, and was assessed on a further five cases before the study. The two specialist registrars were trained on the 3-day course and assessed for competence on five cases, and so were less experienced. However, this was a pragmatic study of NHS practice to test the reality of implementing a therapy which could be delivered on a wide-scale basis, by a variety of practitioners with varying levels of expertise. Both sites had a nominated senior CBT supervisor paid by the trial to undertake regular supervision of CBT treatment. Quality control measures of CBT were undertaken throughout the trial, in addition to the primary outcome measure of well-being and the secondary outcomes measures of mental state. Health economic measures were undertaken by the study team by specialist staff funded from within the project grant and attached to the Centre for the Economics of Mental Health Research Department, Institute of Psychiatry, Kings College, London. The patients were ascertained in Cambridge from outpatients' services serving approximately 367,000 people in South Cambridgeshire and North Essex. A small number of cases (n = 4) were obtained from outpatient services in Huntingdon serving a population of about 150,000. Four clinics were involved in Manchester, serving a total population of approximately 831,000. In addition, in the first year of the trial, four cases were recruited from an inpatient adolescent unit who were not receiving CBT or SSRIs and had not previously been shown to be resistant to these treatments.

Each subject and one adult with parental responsibility provided written informed consent to participate. The trial was approved and monitored by the Multi-Centre Research Ethics Committee and all relevant Local Research Ethics Committees; scientific monitoring was provided by a 6-monthly steering committee consisting of three senior clinician scientists (Professor J Hill, Liverpool University, and Professor W Deakin and Professor G Dunn, Manchester University in the UK, and Professor S Kutcher, Dalhousie University, Nova Scotia, Canada). The NHS Research and Development Coordinating Centre for Health Technology Assessment (HTA) audited progress and quality of study throughout.

The methods and procedures of recruitment and assessment throughout the trial were systematically used throughout the clinical centres in both sites. Differences that may have a bearing on the trial results are specifically referred to in the appropriate sections including data analysis.

Recruitment

Subjects were recruited as follows: referral letters to study clinics were read by the trial psychiatrist to identify prospective patients who may meet inclusion criteria, and referrals were received from clinicians on current patients deemed to meet study criteria. All these putative trial patients were selected for full research assessment.

Inclusion criteria

The inclusion criteria were as follows:

- Aged 11–17 years inclusive and both sexes.

- At least four DSM-IV depressive symptoms (including one core mood symptom of sadness, irritability or anhedonia) occurred during the same 2-week period and was present on assessment.
- Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) score of ⩾7. This score reflects at least one area of 13 evaluated in this measure where the adolescent is experiencing moderate to severe personal difficulties.

Adolescents with current or past suicidal acts or intent were included, even if they were deemed to be at high risk of a suicidal act. All co-morbidity cases (apart from schizophrenia or bipolar disorder) were included.

Patients who met the inclusion criteria and had already been started on an SSRI within 1 month before randomisation were included.

Prior treatment with an SSRI or CBT did not result in exclusion.

Exclusion criteria

The exclusion criteria were as follows:

- Depressed patients aged under 11 years of either sex.
- Patients with co-morbid schizophrenia or bipolar disorder.
- Cases that required immediate admission.
- Current pregnancy or the possibility of becoming pregnant (i.e. unreliable contraception use).
- Clinically overt learning disability (formal testing not undertaken).
- Participants and/or carers were unable to complete research questionnaires.
- Prior sensitivity or allergy to SSRIs, using another medication which may interact with SSRI, a medical condition where use of an SSRI was contraindicated.
- Previous optimal treatment with both an SSRI and CBT with no effect.

All other forms of ongoing psychiatric treatment were permitted during the study period except for CBT if the subject was randomised to the SSRI alone arm of the study.

Adolescents with current or past suicidal acts or intent were not excluded from the study, even if they were deemed to be at 'high suicidal risk'.

Prerandomisation intervention

Systematic assessment and subsequent classification of the type, nature and characteristics of the presenting complaints contributes to the effective prediction of recovery, relapse and persisting disorders.[28–30] Some individuals will, however, remit rapidly and require minimal interventions. This is due in part to depressed patients being referred at different points in their natural history. The objectives of the study may be difficult to achieve if cases about to remit at the time of clinical assessment were included.

In order to ensure that the study recruited cases of non-remitting depression, most eligible adolescents and their family members were offered a brief initial supportive and educational intervention by the trial psychiatrists. This consisted of a minimum of two sessions, prior to the research assessment and randomisation. Cases were excluded if, after this intervention, they were improved (defined as no longer meeting clinical inclusion criteria).

Thirty-four adolescents with proven non-remitting depression did not receive a brief initial intervention (BII) by the trial psychiatrists, as they had already received a psychosocial intervention for depression prior to referral to the trial team.

Twenty-two cases were deemed by the trial psychiatrists to be particularly severe [Children's Global Assessment Scale (CGAS) <40, reflecting major impairment in functioning in several areas and patients unable to function entirely in one of these areas]. Such subjects were permitted to bypass the BII in order to enter the trial as soon as possible. Our sample was significantly impaired and suicidal and many of the subjects who were included in this trial would have been excluded in other trials of depression. For example, we randomised cases of mood congruent psychosis, recent cases of attempted suicide, in addition to current active suicidal intent. Some adolescents were also refusing to eat or drink and were mute and significantly withdrawn. Therefore, if the level of risk was deemed to be high and/or the adolescent was not able to engage in psychological treatment due to the severity of the depression, these subjects were started on an SSRI immediately. As this was a pragmatic trial, high levels of risk had to be managed in the safest way possible, as would be done in the NHS. Most importantly, we considered it vital that these patients with severe symptoms could be included in the trial, as they are normally excluded from such trials.

A further 29 subjects were excluded from BII as they were already on an antidepressant. The majority of these had already been treated in CAMHS services and would have received psychosocial interventions prior to medication, although some patients would have come from GPs prior to the Committee on Safety in Medicines warnings regarding SSRIs in 2003. These last few subjects may have had a higher rate of spontaneous remission, but they accounted for only a small number of those bypassing BII, would have been randomly distributed between arms and are therefore unlikely to have significantly affected the differences between groups or the overall outcomes.

Chapter 3

Measures

A multimethod measurement approach of current mental state and psychosocial impairment was used, incorporating both respondent- and interviewer-based assessments.

Psychopathology

Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL)

The Kiddie-SADS Present and Lifetime (PL) version[31] was used to establish the presence of DSM-IV diagnoses at baseline and 12 and 28 weeks of follow-up. Each symptom is rated on a four-point scale of 0–3, with 2 being sub-threshold and 3 being a clinically relevant symptom. Only symptoms rated as 3 were taken as clinically significant and DSM-IV criteria were used for major and minor depression. Inter-interviewer agreement on the presence or absence of diagnoses has previously been assessed as satisfactory in adolescents with current mental illness (kappa, range for all diagnoses 0.7–0.85).[28] All minor depressions included in the study had four clinically significant symptoms with duration ranging from 8 weeks to 48 months and CGAS scores ranging from 30 to 54, indicating clinically meaningful impairment.

Mood and Feelings Questionnaire (MFQ)

The MFQ is a 33-item self-report measure of current depressive symptoms. The instrument is designed to cover symptom areas specified in DSM-IV for major depressive disorder.[32,33] It has good test–retest reliability (Pearson's $r = 0.78$),[34] an α coefficient of 0.82 and discriminant validity for detecting major and minor depressions in clinical adolescent samples.[35] The MFQ is sensitive to change in depression over time (weeks and months) in adolescents.[29,30]

Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA)

The HoNOSCA were used as the primary outcome measure. HoNOSCA instrument is a routine outcome measurement tool that assesses the behaviours, impairments, symptoms and social functioning of children and adolescents with mental health problems.[36] It provides a global quantitative measure of an individual's current mental health status. The instrument consists of 13 scales. Each scale is interviewer rated on a score between 0 and 4 (total range 0–52). The higher the score, the greater the level of overall mental health problems within the adolescent. The measure is sensitive to change in mental state and psychosocial functioning over a brief (weeks and a few months) period.[37–39]

Clinical global improvement scale

A clinical global improvement scale was also completed by the interviewer after the HoNOSCA assessment. This is an ordinal measure of improvement completed at 6, 12 and 28 weeks by the independent evaluators blind to clinical assessment.[40] All participants are asked how they had been feeling overall in the last month. They were asked whether things had got better or worse and what had changed on a scale rating from 1 (very much improved) to 7 (very much worse).

Children's Global Assessment Scale (CGAS)

The CGAS is an interviewer-based measure of current psychosocial impairment designed to be used in conjunction with a formal mental state assessment.[41] The measure records the overall impression gained by the interviewer regarding the patient's current level of psychosocial functioning. The measure rates current functioning on a scale of 0–100 on a hypothetical continuum of health (100 = entirely healthy)–illness (0 = entirely unhealthy). Scores below 61 index children with potential mental health problems as follows: 60–51, variable functioning with sporadic difficulties; 50–41, moderate degree of interference of functioning; 40–31, major impairments in most areas; 30–21, unable to function; <20, needs considerable or constant supervision. Studies on the inter-rater reliability on the CGAS showed fair to substantial intraclass correlations of 0.59–0.90.[42,43]

Revised Children's Depression Rating Scale (CDRS-R)

Modelled after the Hamilton Rating Scale for Depression, the CDRS-R is a clinical interview tool designed for assessing depressive symptoms in

children and adolescents.[44] The CDRS-R helps clinicians to rate 17 symptom areas: impaired schoolwork, difficulty having fun, social withdrawal, appetite disturbance, sleep disturbance, excessive fatigue, physical complaints, irritability, excessive guilt, low self-esteem, depressed feelings, morbid ideas, suicidal ideas, excessive weeping, depressed facial affect, listless speech and hypoactivity. It is used to diagnose depression and can be repeated to measure response to treatments. CDRS-R can be administered in 15–20 minutes. The instrument has acceptable reliability in clinic settings and is sensitive to change.[45,46]

Suicidality

All acts of self-harm, including attempted suicide and non-suicidal self-cutting, and suicidal thoughts were asked about and recorded. The suicidality items from the K-SADS-PL scale were used to rate suicidality at each research assessment. In view of the importance of suicidality, the more detailed History of Suicidality/Self-Harm section of the K-SADS-L[47] was added 19 months after the start of the trial, to be completed in retrospect at baseline and again at 28 weeks. We asked all participants (53 for baseline assessment, 12 for final assessment) who had already completed these assessments to complete this questionnaire retrospectively; we were unable to obtain this information from 28 subjects at baseline.

Adverse events

Adverse events were recorded at each assessment interview. Respondents and their parents were also asked to complete a check-list noting if any of the following had occurred at least once over the defined time period at baseline and again at 4 weeks: drowsiness or feeling tired; blurred vision; dry mouth; headaches; feeling restless; muscle twitching (tics); pain in the arms or legs; loss of appetite; feeling sick; poor sleep; loose stools; feeling faint or fainting; rashes; creeping feeling on the skin; feeling easily upset.

Quality of therapy

Audiotapes of each CBT session were rated using the Cognitive Therapy Scale.[48] This scale has been shown to possess adequate reliability and validity in adults.[48] No specific scale exists for adolescents; therefore, the scale was modified to incorporate the developmental stage and ability of the adolescent in CBT. General interview procedures, interpersonal effectiveness, specific CBT techniques, additional considerations and overall ratings were scored. The instrument is a seven-point Likert-type scale and the mid-point of the scale (score 3) is generally accepted as the minimum level of therapist competence.

Compliance scale

Adolescents and parents were asked about compliance with medication at each medication review. Compliance was rated on a Likert-type scale of 1–8, where a score of 1 represented no compliance, 3 was some compliance, 5 was considerable compliance and 8 represented full compliance. A similar scale was used to rate compliance with CBT. This assessed compliance within the session and also with homework tasks.

Psychosocial evaluation

General Health Questionnaire (GHQ-28)

This was completed by both parents where possible at baseline and 28 weeks. This questionnaire consists of a 28-item self-report ascertaining whether the respondent has experienced a particular symptom or behaviour over the past week.[48] This version of the GHQ assesses four subscales: somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. This measure was scored using Likert scoring styles 0–1–2–3. Total scores can be used to reflect level of mental health and subscales to denote the putative symptom areas.

Expectancy/helped scale

Children were asked to rate the following question 'How much do you think the treatment will help/has helped **you**?' The parent scale consisted of two questions that were rated: 'How much do you think the treatment will help/has helped **your child**?' and 'how much do you think the treatment will help/has helped **you**? Questions were rated on an eight-point scale ranging from 'not at all' to 'a great deal'. This was completed at the end of the trial.

Target problems

The target problems scale was completed by the child at baseline 6, 12 and 28 weeks. The child identified two problems they were faced with at the time of the baseline assessment. These two problems were then rated at each outcome assessment in terms of how much the problems upset them or interfered with their life and their progress to achieving their target of overcoming the problem. This was rated on an eight-point scale from 'does not' to 'very severely' interferes and 'excellent/complete success' to 'nil/no success'.

Leyton short-form self-report questionnaire

The Leyton short form is an 11-item self-report screening instrument measuring current symptoms for obsessive compulsive disorder.[49] Children completed this measure at all outcome assessments (0, 6, 12 and 28 weeks).

Friendship questionnaires

These were completed by the child and the parent at baseline and 28 weeks. The child questionnaire asked about their friendships and the parent questionnaire asked parents to comment on their children's friendships. The instrument assesses the number, quality and frequency of friendship exposure. Both questionnaires consisted of the same eight questions, with each scored on a four-point scale ranging from 0 to 32, with the lower the score the less competent their current friendships. An interviewer judgement on the overall quality of friendships (good, moderate or poor) was also made with the child at the time of the assessments. Reliability for the scale is good (test–retest in 1 month = 0.9; inter-rater agreement on overall quality kappa = 0.8).

Family Functioning Questionnaire

Parents and children completed a questionnaire (the Family Assessment Device) at baseline and 28 weeks. The questionnaire consists of 12 statements about families, which are rated on a four-point scale from 'strongly agree' to strongly disagree'.[50,51] Reliability for the scale is good (test–retest in 1 month = 0.82).

Recent life events

This quasi-interview measure was completed by both the parent and child at baseline and 28 weeks. Life events were identified by the person completing the questionnaire and it was noted how many months before the interview the event had taken place and the degree of undesirability on the self on a five-point scale (severely, moderately, mildly undesirable, not undesirable, desirable). Following the completion of this questionnaire, the outcome assessors categorised the events as danger to self, danger to others, personal disappointment or permanent losses (death of relative or friend, pet or an exit event where total loss of contact occurred, e.g. moving country). This interview has good reliability and validity in this age range.[13]

Health-related quality of life (HRQoL)

HRQoL was assessed using the EQ-5D, a non-disease-specific measure for describing and valuing HRQoL.[52] The measure includes a rating of own health in five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a rating of own health by means of a visual analogue scale (0–100). It has been extensively used and its psychometric properties are adequate.[52,53]

Service use and costs

The economic evaluation took a broad service-providing perspective, including that of the health, social services, education, voluntary and private sectors. Travel costs to intervention sessions and productivity losses of the primary carer resulting from their child's illness were also recorded. Economic information was collected in interview at baseline and 12 and 28 weeks using the Child and Adolescent Service Use Schedule (CA-SUS), developed by the authors in previous research with young people and adapted for the purpose of the current study.[54–56] At baseline, information covered the previous 6 months. At each of the follow-up interviews, service use since the previous interview was recorded; in this way, the entire period from baseline to final follow-up was covered. Data on the trial interventions, CBT and case management/medication monitoring were collected from clinical records to avoid patients revealing their treatment group to the research assessors.

All unit costs were for the financial year 2003–4 and are reported in UK pounds sterling. Discounting was not necessary due to the short-term nature of the trial. Intervention sessions (monitoring of medication for all young people plus CBT for the combination therapy group) were costed on the basis of the salary of the professional who took the session. Costs included relevant on-costs (employer's national insurance and superannuation contributions) and overheads (administrative, managerial and capital).[57] Intervention sessions lasted approximately 55 minutes for the SSRI + CBT group and 30 minutes for the SSRI group. Indirect time was included using information provided by the trial therapists on the ratio of direct face-to-face contact to all other activities. Although the time the therapists spent in supervision is included in these calculations, supervisor costs were excluded due to difficulties in accurately separating supervision for the two trial groups. Supervisor costs were estimated and explored in sensitivity analysis. Intervention costs were calculated on the basis of the number of sessions attended; the inclusion of the cost of non-attendance was explored in sensitivity analysis. The costs of the initial clinical assessment and brief prerandomisation intervention were not included as these activities took place before randomisation.

Costs of SSRI medication and any other psychotropic medication were taken from the BNF.[58] Hospital contacts were costed using NHS Reference Costs.[59] Unit costs of community services, including health, social, voluntary and private sector services, were taken from national publications.[60] The costs of schooling came from a number of sources.[61–63] Productivity losses were calculated using the human capital approach, which involves multiplying days off work due to illness by the individual's salary level.[64]

Chapter 4

Ascertainment

Recruitment characteristics

The study sample recruitment procedure is shown in *Figure 1*.

A total of 510 patients between 2000 and 2004 were offered a screening clinical assessment for possible MDD. Of these, 261 (51%) were excluded. Reasons for exclusion were that 109 (21%) did not meet criteria for MDD; 48 (9%) failed to attend interview; 39 (7%) expressed concern about SSRIs and 38 (7%) refused to participate; 20 (3%) were ineligible for other reasons. A further six (1%) cases required admission due to psychosis, severity of depression or were unable to provide written informed consent.

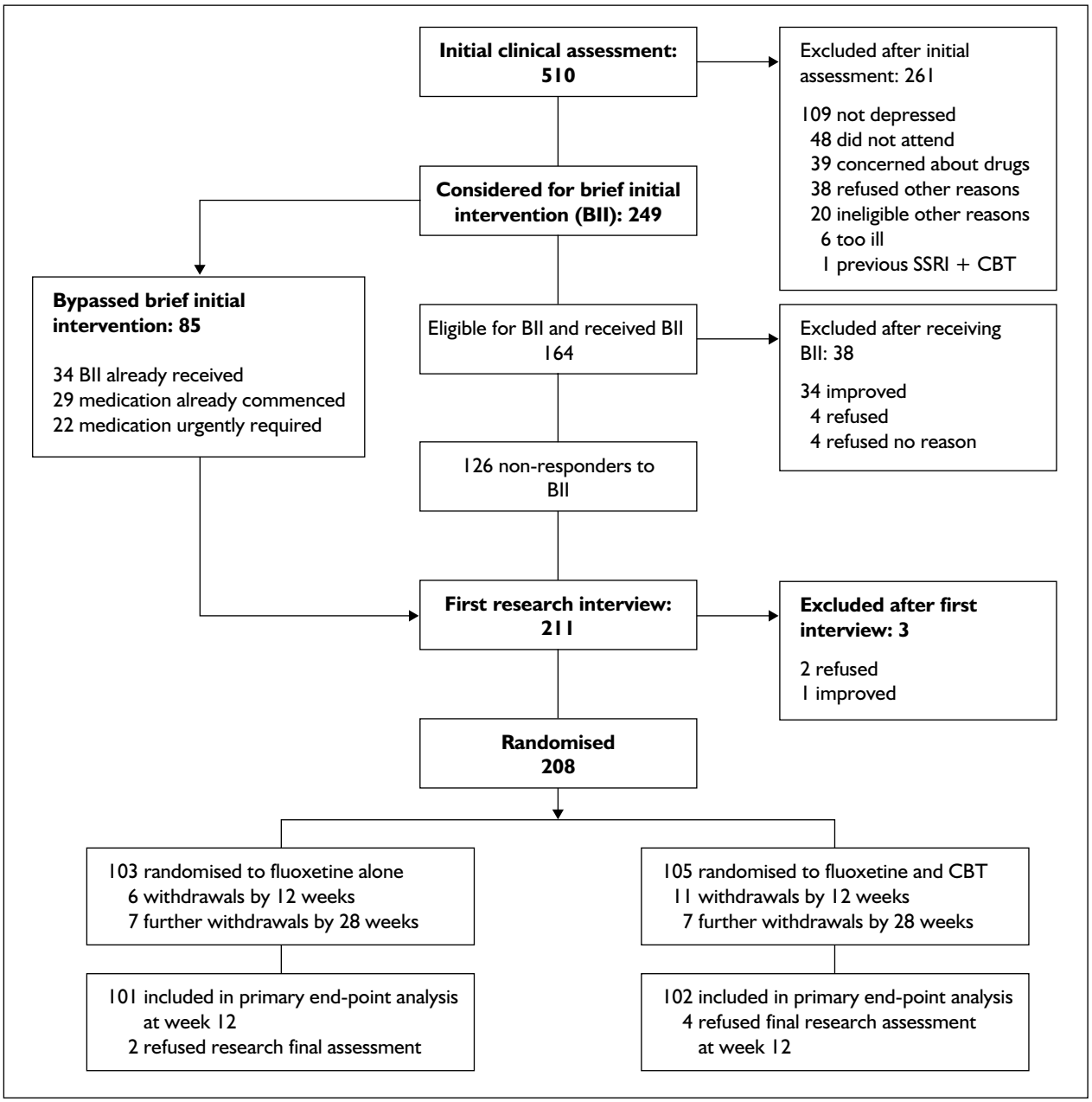

FIGURE 1 *Recruitment procedure*

Of the 249 (49%) who met the inclusion criteria, all were considered for the BII, of whom 164 (65%) received a BII by a trial psychiatrist. Of these, 38 (22% given BII) did not proceed to randomisation.

A further 85 (34%) of those meeting the inclusion criteria bypassed the BII by the trial psychiatrist and proceeded straight to randomisation. The reasons for bypassing the BII were that 29 had already commenced medication within the previous month, 22 were deemed to be too ill for BII and in urgent need of medication (e.g. mood congruent psychosis; actively suicidal; refusing food; significantly withdrawn and currently unable to participate in psychological treatment) and 35 had already received and not responded to psychosocial interventions given in routine CAMHS and therefore a further BII was unjustifiable. As this was a pragmatic trial and it was considered important to ensure that the most severe cases could also be included, unlike previous trials, these high-risk cases had to be managed in as safe a way as possible, and therefore medication was not withheld if it was considered essential to safe management and unlikely that there would be spontaneous remission or a quick response to a BII. Of the patients who had already commenced an SSRI, the majority were referred from CAMHS and would have already had a psychosocial intervention.

Prior to the safety warnings on SSRIs in 2003, some of these patients would have come directly from GPs; therefore, some of the 29 patients who had already commenced an SSRI would not have had a CAMHS psychosocial intervention.

Hence in total 211 (85% of those who met inclusion criteria = 126 BII non-responders + 34 bypassed BII as had psychosocial interventions in CAMHS + 22 deemed too ill for BII + 29 SSRI already commenced) proceeded to the first research interview. At this stage, three participants dropped out (two refusals to enter the trial and one improved and no longer met the inclusion criteria).

Hence 208 were randomised to either SSRI alone (n = 102) or SSRI + CBT (n = 106). Of the subjects randomised, 192 (92%) met the criteria for a definite MDD and 16 (8%) met criteria for minor depression. There was no significant difference in the level of impairment (CGAS rating) at entry between the major and the minor cases [minor, CGAS mean 42.0, standard deviation (SD) 6.6, median 45; major, mean 40.6, SD 5.5, median 40; Mann–Whitney $Z = -1.1$, $p = 0.26$.), but major cases were significantly more impaired on the HoNOSCA at entry (minor, mean 22, SD 3.9; major, mean 25.6, SD 5.6; $t = 2.53$, $p = 0.012$).

Chapter 5
Trial procedures

Randomisation and blinding

After the brief initial intervention (if appropriate) and the baseline research assessment, the study psychiatrist telephoned an independent centre, the Department of Medical Statistics at the Christie Hospital in Manchester, for randomisation. Participants were randomised to SSRI + CBT or SSRI only by a 1:1 treatment allocation ratio. Stochastic minimisation was used to ensure balance on severity, centre, sex, co-morbid behavioural disorder (probable or definite oppositional defiant disorder or conduct disorder) and age.

As the study compared CBT with non-CBT, participants and treating clinicians could not be blind to treatment. Outcome assessments were done by independent evaluators blind to treatment assignment. Specific instructions were given to participants, parents and treating clinicians not to disclose treatment assignment to the blinded evaluator. To measure the adequacy of blinding, evaluators were asked to guess treatment assignment after the final outcome assessment for each participant.

Treatments were designed to reflect accurately real-life best practice in NHS child and adolescent mental health clinics. Treatment manuals for both treatment arms were used to aid dissemination into clinical practice, standardise the intervention between therapists and form the basis for audiotape ratings of adherence to the intervention. Since this was a pragmatic study, manuals were guides and principles of treatment which could easily be incorporated into NHS practice, rather than rigid session-by-session instructions.

The randomised participants were treated in routine outpatient settings by the trial psychiatrists who delivered the treatments to both arms. The precise details of additional CAMHS services received by the trial participants were not systematically assessed. Throughout, trial psychiatrists were supervised fortnightly by a chartered psychologist who was a CBT trainer, on the quality of CBT delivered. The CBT therapists within the CAMHS services were experienced in delivering these treatments in outpatient settings.

As trial psychiatrists were responsible for treatment in both arms and also administered much of the CBT, efforts were made to ensure there was no cross-contamination of CBT treatment. All the psychiatrists were part of the research team and were highly aware of the importance of treatment fidelity. Although some principles of CBT treatment would have been used as part of routine clinical care (principally behavioural activation), this is part of standard NHS care and would be far removed from the structured, collaborative approach used in CBT. The routine clinical care treatment would mainly take the form of advice, rather than collaborative goal-setting, homework, rewards and exploration and challenging of negative cognitions. There would be no explanation of the CBT model, and the sessions offered were shorter and fewer. In addition, the SSRI and clinical care alone sessions were audiotaped for further analysis of the treatment components.

Both trial psychiatrists received weekly case management supervision from senior child psychiatrists (RH in Manchester, RK in Cambridge) with medical responsibility for the patients in the study. Treatments were delivered in both arms for 28 weeks.

SSRI-only treatment arm

All participants were seen regularly for prescription and monitoring of medication by one of the study psychiatrists. All psychiatrists met regularly to discuss medication use in the study and received regular supervision. Fluoxetine was chosen as the primary SSRI throughout the study, as it was the only SSRI with RCT evidence for efficacy at the start of the study. The initial dosage was 10 mg/day, to be increased to 20 mg/day if tolerated. If necessary and tolerated, the dose was increased after 6 weeks, up to a maximum of 60 mg/day. If fluoxetine was ineffective, or causing problematic side-effects, other SSRIs were considered on a case-by-case basis, and in line with best available evidence and UK regulatory authority guidance at the time. Subjects already receiving another SSRI at the point of randomisation were allowed to continue on these, but if the SSRI was not effective, the dose was increased or the SSRI was switched to fluoxetine.

SSRI plus CBT treatment arm

In addition to SSRI prescription and monitoring as described above, subjects were offered weekly CBT for 12 weeks in the treatment phase, followed by fortnightly maintenance sessions for the next 12 weeks with a final session at 28 weeks (total 19 sessions). The majority of CBT (75 patients) was provided by the trial psychiatrists who were also monitoring medication. RH had CBT experience and was a co-author of the manual; BD also had CBT experience prior to the study. The psychiatrists (BD, PW, AL) attended the same 3-day CBT for depression training course and were required to have provided supervised CBT for a minimum of five different patients and to have reached pre-agreed competence criteria in five audiotaped sessions before starting therapy for the study. Ten CBT therapists (all course trained) and working either sessionally or full time in the NHS CAMHS services also provided CBT for 31 subjects in the study. All CBT was supervised by fully accredited CBT supervisors working in NHS services and with at least 2 years of experience of treating depressed adolescents with these therapies. If subjects consented, all CBT sessions were audiotaped and a random session for each participant was rated by one of the study psychiatrists to assess quality of the therapy. Twenty of these sessions were also rated by another trial psychiatrist to check inter-rater reliability, which was satisfactory (kappa >0.8).

Twelve subjects received CBT from two therapists. This occurred if a therapist became unavailable, principally as a result of a planned maternity leave, which would have been discussed at the outset with the adolescent. Alternatively, if the principal available therapist was on leave at the time of randomisation, the first few introductory sessions may have been provided by a trial psychiatrist (who had already established a therapeutic relationship with the adolescent) in order to ensure that CBT commenced from the point of randomisation. However, the majority of sessions would have been provided by one therapist. The first scenario would be a common occurrence in the NHS and thus reflect the pragmatic nature of the trial. The second scenario occurred because of the time constraints within an RCT to begin treatment from the point of randomisation, which would in fact deviate from NHS practice, where the patient would wait for the availability of the therapist.

Other interventions

All participants received the standard interventions given to any depressed adolescent in NHS clinics: regular monitoring of mental state; psychoeducation; reflection, support and encouragement to adolescents and their families; problem solving; attention to co-morbidity; and liaison with other professionals, such as teachers and social workers. If necessary, some adolescents were referred to a hospital school. According to the study protocol, the only treatment that could not be given to subjects was CBT in the non-CBT group. In a small number of cases, non-responders in the fluoxetine only arm requested CBT, and this was only given after 12 weeks. Other specific interventions, such as family therapy, could be given. These were kept to a minimum in the first 12 weeks after randomisation.

Therapists rated compliance with medication and CBT at each session. Subjects were asked to bring medication bottles or tablet boxes to each session to facilitate assessment of compliance.

Research assessments

The independent evaluators carried out assessments with the participant and a parent or carer at baseline and 6, 12 and 28 weeks. Assessment took place at home or in clinic, according to participants' wishes. Parent and child mental state evaluations were combined to give a best estimate diagnosis.

The *a priori* primary outcome measure, completed at all assessments, was HoNOSCA. Secondary measures were also collected at all four outcome assessments.

The outcome assessors were graduates in psychology. They received full training in the outcome assessments and inter-rater reliability of the interview-based measures was tested before and during the study between sites. All assessors rated 'gold standard' audiotaped interviews and a selection of each other's interviews, to ensure inter-rater reliability of HoNOSCA and K-SADS-PL rating of kappa >0.75 before and throughout the study. Inter-rater reliability for HoNOSCA (intra-class correlation coefficient) was 0.94 before the study and 0.89 during the study. Inter-rater reliability for diagnosis of depression using K-SADS-PL (kappa) was 0.91 before the study and 0.71 during the study.

Chapter 6

Hypotheses tested

Participants in the SSRI + CBT arm will show a greater improvement in mental health and psychosocial impairment than patients in the SSRI only arm over the course of the trial. Specifically at 6, 12 and 28 weeks compared with the SSRI only group, those receiving SSRI + CBT will:

Primary outcome measure:

1. Show significantly improved HoNOSCA scores (primary outcome measure).

Secondary outcome measures:

2. Have a significantly lower proportion of patients meeting DSM-IV criteria for major or minor depression.
3. Self-report significantly less depressive symptoms.
4. Have significantly lower interviewer-rated depression symptoms.
5. Demonstrate higher levels of social function.

Additional hypotheses:

6. The additional expenditure of CBT over fluoxetine will be offset by the cost benefits of this treatment.
7. Adverse side-effects including suicidality will be significantly less in the SSRI + CBT compared with the SSRI only arm independently of treatment outcome.
8. Co-morbidity characteristics at entry will exert no effects on treatment efficacy in either arm.
9. Initial severity, duration and impairment of depression at entry will exert no effects on treatment efficacy in either arm.

The study does not test if SSRI only or CBT only is effective in the absence of clinical care as there is no non-treatment or routine care only arm.

Chapter 7

Data analytic strategy

Characteristics of the study sample are reported using standard frequency measures. Where comparisons are made between the groups on categorical measures, non-parametric methods for the assessment of proportions are used. Parametric methods for the comparisons of means at baseline following randomisation are used.

Analysis of clinical outcome measure

The efficacy outcome measures [HoNOSCA, CDRS, MFQ, clinical global improvement (CGI)] were recorded at baseline and 6, 12 and 28 weeks. For HoNOSCA, CDRS and MFQ scores, higher scores represent a 'worse state', hence a negative gradient over time represents improvement. For CGAS, higher scores represent a 'better state', so that a positive gradient for a patient represents improvement over time.

Unless there is a special interpretation of a particular follow-up time point, analyses of longitudinal outcome data should avoid multiple cross-sectional analyses, particularly where there are large numbers of follow-up assessments on each subject.[65] Instead, a longitudinal statistical model should be fitted across follow-up time points. The main statistical analysis used to compare the two interventions was a linear random effects model.[66] This may be thought of as fitting regression lines of outcome against time for each patient with variation between patients represented by differences in the intercept and gradient of these lines. In the resulting statistical model, random effects are included to account for between-patient variation in the intercept and the gradient of the patient-specific lines. Fixed covariates are included to model for systematic differences due to treatment, assessment time point or patient characteristics.

In such a longitudinal model of treatment outcome, a difference between the two treatments can manifest as different mean levels across all time points or in the mean line for each treatment group having different slopes. Where a reduction in outcome values suggests improved outcome, a negative slope corresponds to improving outcome. To test for differences in the rate of improvement between treatments, a time–treatment interaction should be fitted. A non-zero time–treatment interaction corresponds to differences between treatments in the rate of improvement. Second, differences in mean level over time would correspond to a systematic difference between treatments in the follow-up. To test for differences in mean level and gradient between intervention groups, models with and without these terms were compared using a likelihood ratio test. Rather than fitting a model across both baseline and follow-up responses, the **baseline** value of the outcome measure was included as a covariate. This is usually more efficient than including the baseline as a response variable and simplifies interpretation where there are several follow-up assessments. Using baseline as a covariate also removes the problem of non-linearity that can occur if change from baseline to the first follow-up assessment tends to be large compared with change between subsequent assessments. In addition to treatment group, models include as covariates, time from randomisation to each assessment in weeks, sex, age at randomisation in years, presence of a behavioural disorder and centre (Manchester or Cambridge). Baseline values of HoNOSCA, CDRS(t), MFQ and CGAS were included as covariates for all models to improve efficiency. Normal probability plots were used to check distributional assumptions of the model for residuals of within and between subject variance terms.

The CGI is a seven-point ordered categorical scale. This was analysed using an ordinal logistic regression model with random intercept and gradient terms on the log-odds scale.

To examine the effect of treatment on suicidal behaviour and self harm, Question 3 from HoNOSCA and items DE4–DE8 from K-SADS-PL were used. The HoNOSCA item was a five-point scale. An ordinal logistic regression model with random intercept and gradient terms on the log-odds scale was used to analyse this. The items from K-SADS-PL have as values scales points 0, 1, 2 (sub-threshold) and 3 (clinical threshold). The

proportion of patients rated/rating clinical threshold was modelled using a logistic regression model with a random intercept.

Therapist effects

In randomised trials of interventions involving talking therapies, it has been argued that there may be variations in patient outcomes between therapists,[67,68] sometimes referred to as clustering. To account for this, the effect of therapist may be included in statistical analysis by adding a random effect term to the model. As with cluster randomised trials, failure to account for therapist variations in the analysis can lead to overly precise estimates of the treatment effect. In this trial, the therapist effect might be expected to apply to the SSRI + CBT intervention arm. A random effect term was included for the CBT therapist in the SSRI + CBT treatment arm in the longitudinal model outlined above. This was added so that the effect of therapist was modelled by variations in the intercept.

The proportion of the total variance due to therapists, which can be called the intra-therapist correlation coefficient (ITCC), varies with time due to the random gradient term in the model. For comparative purposes, the ITCC was calculated as

$$\text{ITCC} = \sigma_T^2/(\sigma_T^2 + \sigma_P^2 + \sigma_\varepsilon^2)$$

where σ_T^2 is the between-therapist variance, σ_P^2 is the patient-level random intercept variance and σ_ε^2 is the residual error variance.

Subgroup and secondary analyses

Severity of depression prior to treatment may influence the treatment effect. The appropriate method for testing for such an effect is to add a treatment–severity interaction to the model. Baseline CGAS was used for this analysis (cut-off 40).

In order to assess the quality of CBT delivered, an assessment was carried out of a tape recording of a CBT treatment session. The quality score was included in a longitudinal model of outcome to ascertain whether quality of CBT was associated with outcome.

Missing data and intention-to-treat (ITT)

The primary statistical analysis was, according to the ITT principle, subject to the availability of follow-up data. In a randomised trial involving outpatients, it is inevitable that there will be some missing data at follow-up due to patient withdrawal, loss to follow-up or incomplete data recording. Non-response may bias the estimate of the treatment effect unless the missing data can be said to be **missing completely at random**. If non-response is predictable from baseline variable, inclusion of predictors of non-response as covariates will reduce biases in estimates where the missing data can be said to be **missing at random**. Whether data are **missing at random** as compared with **informatively missing** is an untestable assumption without additional information. Hence in the analysis, data are assumed to be **missing at random**. It is therefore important to obtain data that are as complete as possible. To this end, great effort was made to achieve as complete a response as possible. Intensive efforts were made to follow up all participants, including those who had dropped out of treatment, and participants were paid £10 for each research interview. At the analysis stage, a logistic regression model was used to identify predictors of non-response. As part of the analysis plan, predictors of non-response were included as covariates in the main statistical analysis of treatment effects.

Statistical analyses were carried out using STATA Release 9 (STATA Statistical Software, Release 9, StataCorp, College Station, TX, USA, 2005).

Economic analyses

All economic analyses were carried out on an ITT basis using a statistical analysis plan drawn up prior to the analysis of the data. Initially, traditional statistical tests for differences in total costs were undertaken. Although costs were not normally distributed, analyses compared the mean costs in the two groups using the standard *t*-test with ordinary least-squares regression used for adjusted analyses and the validity of results was confirmed using bootstrapping.[69] The advantage of this approach, as opposed to logarithmic transformation or non-parametric tests, is the ability to make inferences about the mean.[70]

The primary analysis was of total costs per young person over 28 weeks, but carer costs and productivity losses are also presented. Multiple regression was used to adjust for the following prespecified baseline characteristics: gender, age at randomisation, treatment centre, baseline costs, HoNOSCA score, severity of illness measured using the CGAS and co-morbid behavioural

disorder as determined by the K-SADS-PL. Subgroup analyses by centre and severity of illness were performed using tests of interaction. The impact of drop-out was assessed by comparing the baseline characteristics of patients who had missing data with those of patients who had full economic data.

Issues of statistical significance were then put to one side in order to explore the relative cost-effectiveness of the interventions in a decision-making context. Cost-effectiveness was explored over the 28-week follow-up period through the calculation of incremental cost-effectiveness ratios (ICERs) – the difference in mean costs divided by the difference in mean effects.[71] Repeat resampling from the costs and effectiveness data (bootstrapping) was used to generate a distribution of mean costs and effects for the two treatments.[69] These distributions were used to calculate the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (ceiling ratio, λ) that a decision-maker might be willing to pay for either a unit improvement in HoNOSCA score or quality-adjusted life-years (QALYs). To explore the uncertainty that exists around the estimates of mean costs and effects as a result of sampling variation and uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would consider acceptable, cost-effectiveness acceptability curves (CEACs) are presented by plotting these probabilities for a range of possible values of the ceiling ratio.[71,72]

A cost function analysis was undertaken to explore and quantify the impact of individual baseline characteristics on total costs at follow-up. The literature on factors that influence resource use and costs in young people was reviewed in order to identify potential predictors of total cost.[73,74] Univariate associations between each of the specified predictors and total monthly costs were explored in linear regression. For continuous variables, although analyses were carried out on continuous data, results are presented in two groups split at the median. Multiple regression was used to reduce the variable set to those factors independently associated with costs, using a process outlined by Byford and colleagues.[75] The multiple regression initially included all variables that had important univariate associations with cost, discarding from the model all variables that were no longer found to be important. Variables that did not have a univariate association with cost were added and retained if they added significantly to the model, or were otherwise discarded. The model finally arrived at was checked to ensure that no variables excluded would add significantly to it. A significance level of around 10% was used, although not strictly applied to avoid incorrectly dismissing variables significantly related to cost in multiple regression.

Chapter 8
Results

Baseline characteristics of treatment groups

The mean age of the sample was 14.0 years (SD 1.5). There were 154 (74%) females and 54 (26%) males. Within the study sample, 187 (97%) of 194 documented were of white European origin. Amongst the study sample, 98/208 (47%) adolescents had a biological parent living at another address.

The overall degree of psychosocial impairment and diagnostic profile at first research assessment prior to randomisation for all 208 participants is shown in *Table 1*.

The mean number of symptoms for the SSRI + CBT and SSRI only groups at randomisation were 6.6 (SD 1.5) and 6.4 (SD 1.4), respectively (Mann–Whitney $Z = -0.8$, $p = 0.4$). Overall at the time of randomisation, the measures are convergent in indicating a severely depressed study population.

Within the study sample, 177 (88.5%) were concurrently comorbid for at least one other psychiatric disorder (*Table 2*). The most frequent were social phobia and obsessive compulsive disorder. About one-third had a disruptive behaviour disorder.

Withdrawals

The treatment pathway for completers and non-completers is shown in *Figure 2*.

Research assessment withdrawals

Of the 208 randomised patients, six (3%) withdrew prior to the 12-week end-point of the trial. Primary end-point data (at 12 weeks) were therefore available on 202 (96%) subjects. Six-week data were available on three of the withdrawn subjects. At 28 weeks, 15 research assessments were not completed. Overall, only two cases (1%) did not complete any assessments after baseline, resulting in 206 (99%) participants with at least one research assessment post-baseline.

Treatment withdrawals before 12 weeks for clinical reasons

Seven patients were formally withdrawn from treatment prior to 12 weeks for clinical reasons: three required admission for suicidality or self-harm (all in the CBT arm), one failed to improve (CBT arm), one had a fit which was possibly

TABLE 1 *Impairment at first research assessment*

Measure	Mean score (SD)		
	Total sample	**Fluoxetine only**	**Fluoxetine + CBT**
HoNOSCA[a]	25.3 (5.5)	25.5 (5.6)	25.1 (5.5)
CGAS[a]	40.7 (6.9)	40.3 (6.3)	41.6 (6.0)
CDRS-R (raw score)	58.8 (10.4)	59.0 (9.5)	58.9 (10.5)
CDRS-R (*t*-score)[a]	75.0 (7.4)	75.3 (6.7)	75.1 (6.7)
MFQ[b]	38.2 (12.2)	38.2 (12.7)	37.9 (11.9)
	***n* (%)**		
Psychotic symptoms	16 (8)	10 (10)	6 (6)
	Median (min.–max.)		
Duration of depression (weeks)	40 (3–624)	52 (4–624)	32 (3–260)

[a] Observer rated.
[b] Respondent rated.

TABLE 2 *Co-morbidity at first research assessment*

Co-morbid diagnosis	Fluoxetine only (*n* = 103)	Fluoxetine + CBT (*n* = 105)	Total (*n* = 208)
Social phobia	49 (48.03%)	43 (40.56%)	92 (44.23%)
Obsessive compulsive disorder	37 (36.27%)	42 (39.62%)	79 (37.98%)
Post-traumatic stress disorder	36 (35.29%)	42 (39.62%)	78 (37.5%)
Agoraphobia	29 (28.43%)	36 (33.96%)	65 (31.25%)
Separation anxiety disorder	28 (27.45%)	31 (29.24%)	59 (28.36%)
Specific phobia	22 (21.56%)	25 (25.58%)	47 (22.59%)
Conduct disorder	17 (16.66%)	18 (16.98%)	35 (16.82%)
Panic disorder (without agoraphobia)	14 (13.72%)	21 (19.81%)	35 (16.82%)
Oppositional defiant disorder	13 (12.74%)	17 (16.03%)	30 (14.42%)
Generalised anxiety disorder	13 (12.74%)	19 (17.92%)	32 (15.38%)
Panic disorder (with agoraphobia)	13 (12.74%)	20 (18.86%)	33 (15.86%)
Attention deficit hyperactivity disorder	6 (5.88%)	5 (4.71%)	11 (5.28%)
Bulimia nervosa	4 (3.92%)	8 (7.54%)	12 (5.76%)
Alcohol abuse	4 (3.92%)	1 (0.94%)	5 (2.40%)
Transient tic disorder	3 (2.94%)	2 (1.88%)	5 (2.40%)
Tourettes	2 (1.96%)	2 (1.88%)	4 (1.92%)
Alcohol dependence	2 (1.96%)	1 (0.94%)	3 (1.44%)
Chronic motor or vocal tic disorder	1 (0.98%)	2 (1.88%)	3 (1.44%)
Anorexia nervosa	0 (0%)	1 (0.94%)	1 (0.48%)
Encopresis	0 (0%)	1 (0.94%)	1 (0.48%)
Enuresis	0 (0%)	1 (0.94%)	1 (0.48%)
Dysthymia	0 (0%)	1 (0.94%)	1 (0.48%)

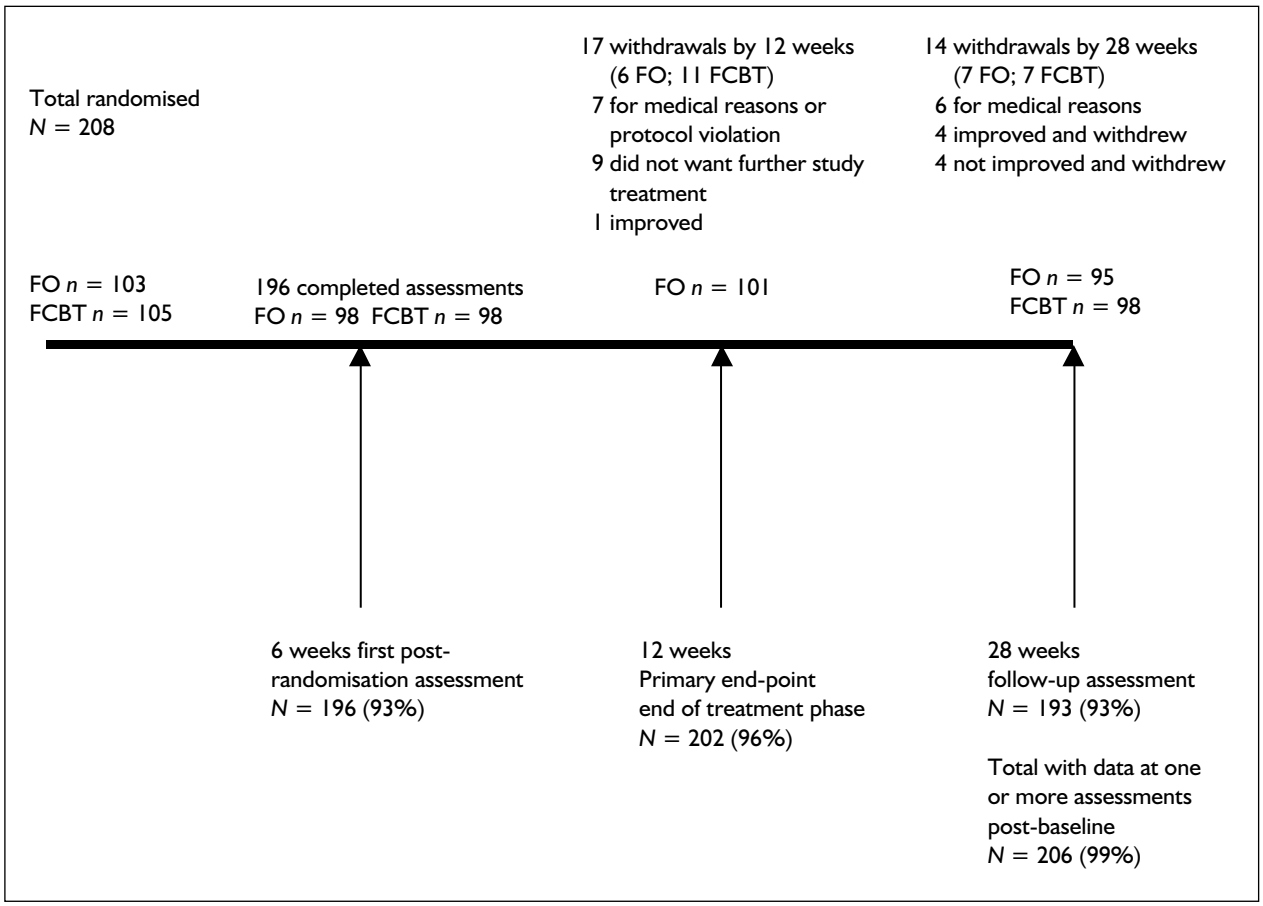

FIGURE 2 *Study assessments and completions. FO, fluoxetine only; FCBT, fluoxetine + CBT.*

secondary to medication (CBT arm), one had an allergic reaction where medication could not be excluded as a possible cause (fluoxetine only arm) and one was a protocol violation (fluoxetine only arm, started on paroxetine by the GP after this SSRI had been contraindicated by the Committee on Safety in Medicines).

Treatment withdrawals before 12 weeks initiated by patient and/or family

Two adolescents formally withdrew from both treatment and research assessments before 12 weeks. One adolescent improved and the other did not want further treatment. Both were in the CBT arm. A further eight adolescents withdrew from treatment before 12 weeks. Three did not want any more treatment, two did not want CBT, two wanted CBT and one did not wish to have a male therapist. Primary end-point assessments were obtained on these eight patients. Six of these cases were in the CBT arm and four in the fluoxetine only arm.

Treatment withdrawals after 12 weeks for clinical reasons

Six adolescents were withdrawn after 12 weeks by clinicians, five of whom were in the fluoxetine only arm. One adolescent was admitted for suicidality, one was psychotic (SSRI + CBT arm), two did not improve, one did not improve and also wanted CBT and one did not improve and there were child protection concerns.

Treatment withdrawals after 12 weeks initiated by patient and/or family

Eight adolescents withdrew from treatment after 12 weeks. Four had improved and did not want any more treatment (three SSRI + CBT, one SSRI only), one was not improving and did not want any further treatment (SSRI + CBT), in one case the family thought the adolescent's behaviour was getting worse (SSRI only), one moved (SSRI + CBT), and the last did not want further treatment (SSRI + CBT).

Attendance

The number of clinical sessions attended by the study participants at 12 weeks is shown in *Table 3*.

TABLE 3 *Number (%) of participants attending for clinical sessions by 12 and 28 weeks and after 12 weeks*

Sessions attended	Fluoxetine only (n = 103)	Fluoxetine + CBT (n = 105)
By 12 weeks[a]		
0	5 (5%)	0
1–3	37 (36%)	12 (11%)
4 or more	61 (59%)	93 (89%)
By 28 weeks[b]		
0	4 (4%)	0
1–3	25 (24%)	9 (9%)
4 or more	74 (72%)	96 (91%)
After 12 weeks[c]		
0	27 (26%)	24 (23%)
1–3	46 (45%)	38 (36%)
4 or more	30 (29%)	43 (41%)

[a] Mann–Whitney U test: $Z = -6.88$, $p < 0.001$.
[b] Mann–Whitney U test: $Z = -5.37$, $p = <0.001$.
[c] Mann–Whitney U Test: $Z = -1.96$, $p = 0.050$.

12-week attendance

SSRI-only arm

The mean number of sessions attended was 4.1 (SD 2.3) at 12 weeks. Five patients did not attend any sessions and 42 attended three or fewer sessions. Sixty-one attended four or more sessions.

SSRI + CBT arm

The mean number of sessions attended (including medication review sessions without CBT) was 7.2 (SD 3.5). No subjects withdrew from treatment completely. Twelve subjects attended 1–3 sessions and 93 attended four or more sessions. The mean number of CBT only sessions (excluding separate medication review sessions) was 6.2 (SD 3.3). Five subjects did not attend any CBT sessions and 13 attended three or fewer. Eighty-seven subjects attended four or more CBT sessions.

Overall, the SSRI + CBT group attended significantly more sessions by 12 weeks than the SSRI only group.

28-week attendance

SSRI-only arm

The mean number of sessions attended by 28 weeks was 6.5 (SD 4.0). Four patients continued not attending any sessions. Twenty-one subjects attended 10 or more sessions. The mean number of additional sessions attended after 12 weeks was 2.4 (SD 2.2). Twenty-seven subjects did not attend any further sessions, and 30 attended an additional four or more sessions.

SSRI + CBT arm

The mean number of sessions attended (including medication review sessions without CBT) was 10.6

(SD 5.7). Fifty-four subjects attended 10 or more sessions. The mean number of additional sessions attended after 12 weeks was 3.4 (SD 3.2). Twenty-four subjects did not attend any further sessions, and 43 attended four or more additional sessions.

The mean number of CBT only sessions (excluding separate medication review sessions) was 9.1 (SD 5.3). Two subjects did not attend any CBT sessions throughout the 28 weeks. Forty-six attended 10 or more sessions. The mean number of additional sessions in the CBT group after 12 weeks was 3.0 (SD 3.1). Twenty-nine subjects did not attend any further CBT sessions after 12 weeks.

Overall, the SSRI + CBT group attended significantly more sessions by 28 weeks than the SSRI only group.

Differences in attendance between Manchester and Cambridge

Of the 149 cases recruited in Manchester, the mean attendance at 12 weeks was 5.2 (SD 3.5), and 7.4 sessions (SD 5.1) from baseline to 28 weeks. In Cambridge, 59 patients were recruited and the mean attendance was 6.7 (SD 2.5) and 11.7 sessions (SD 4.9), respectively.

Attendance at outpatients was significantly greater in Cambridge ($n = 59$) than Manchester ($n = 149$) patients by 12 weeks [6.7 (SD 2.5) versus 5.2 (SD 3.5) sessions, Mann–Whitney, $Z = -5.59$, $p < 0.0001$] and from baseline through to 28 weeks [11.7 (SD 4.9) versus 7.4 (SD 5.1) sessions, Mann–Whitney, $Z = -5.59$, $p < 0.0001$].

In Manchester, five subjects did not attend any sessions by 12 weeks. All subjects attended at least one session in Cambridge.

Quality of CBT

Quality of therapy was rated on 86 of the 105 subjects randomised to CBT (82%). The other subjects were not rated as either the patient refused or did not attend or there were technical difficulties with the recording. The mean score was 57.1 (SD 10.9) out of a possible total of 78. Of the CBT sessions that were rated, 64 patients were treated by psychiatrists and 22 by CBT therapists. The mean score for psychiatrists was 54.7 (SD 10.5) and the mean score for therapists was 64.2 (SD 8.8). This difference was significant ($p = <0.001$). Seven patients scored less than 40. In six of these cases, the patient was rated as uncooperative with therapy, i.e. rated as 0 or 2 on a scale from 0 to 6, where six was a very receptive patient. Of the remaining cases that were rated, only two further subjects were rated as uncooperative with CBT.

Suicidality

Using K-SADS-PL threshold and subthreshold data, at first assessment 154 (63.3%) of the study participants had experienced either occasional or frequent suicidal thoughts, 47 (22.7%) had carried out a suicidal act and 68 (32.8%) had self-harmed over the previous month. This indicates that this was a depressed group at high risk for suicide. According to the History of Suicide Questionnaire, half of the participants interviewed (91 of 180 subjects, 51%) had engaged in at least one suicidal act in the past. Seventy-eight (43%) of adolescents had made a definite or serious suicide attempt in the past. Fifty-seven (32%) participants had self-harmed repeatedly.

Response rates and missing data

Table 4 gives the response rate for each assessment. Compared with similar studies, the non-response rate was low. A logistic regression model was fitted to an indicator variable of loss to follow-up at each assessment (6, 12 and 28 weeks) including sex, age, behavioural disorders [combined conduct ($n = 35$) and oppositional ($n = 30$) disorders], site and baseline values of HoNOSCA, CDRS(t), MFQ and CGAS. There was some evidence that non-response at 28 weeks was higher in younger age groups: the odds ratio for non-response for patients under 15 compared with those 15 years and over was 5.1 [95% confidence interval (CI) 1.1 to 5.1, $p = 0.037$] with a loss to follow-up of 11% (13/114) in the younger compared with 2% (2/94) in the older age group. Statistical analyses of outcome were all adjusted for age, so it is unlikely that this non-response would bias the analysis. The follow-up rate at 28 weeks was 98% (58/59) in Cambridge compared with 91% (135/149) in Manchester, but this difference was not significant ($p = 0.16$). Overall, there was no suggestion that follow-up rates were related to baseline factors.

Table 5 gives the time until each follow-up assessment. As would be expected, some follow-up assessments were obtained after the target date. More than 75% of assessments were obtained within 10 days of the target date.

TABLE 4 *Response rate for primary outcome (HoNOSCA) by assessment and group*

Assessment time (weeks)	Treatment group			
	SSRI only		SSRI + CBT	
	n	Response rate (%)	*n*	Response rate (%)
0 (randomisation)	103		105	
6	98	95	98	93
12	101	98	101	96
28	95	92	98	93

TABLE 5 *Time (weeks) from randomisation until assessment by group*

Assessment time after randomisation (weeks)	SSRI only					SSRI + CBT				
	Median	Min.	25th percentile	75th percentile	Max.	Median	Min.	25th percentile	75th percentile	Max.
6	6.1	4.0	6.0	7.1	10.6	6.3	4.7	6.0	7.3	12.1
12	12.6	8.0	12.0	13.7	18.1	12.4	10.9	12.0	13.0	20.9
28	28.4	21.9	28.0	29.9	50.6	28.2	20.7	28.0	29.1	47.1

Therapist delivering CBT

Fifteen therapists delivered the CBT therapy, with the median number of patients receiving therapy from a particular therapist being five (range 1–29). Twelve of the 103 patients who received CBT did so from more than one therapist. For the purpose of analysis, the therapist who delivered the most sessions for a patient was coded as being that patient's CBT therapist.

Clinical outcomes

Table 6 gives summary statistics for the primary outcome measure HoNOSCA and the secondary quantitative outcomes, CDRS(t), MFQ and CGAS. Mean values for the two treatments were similar at corresponding assessments. All outcome measures showed a substantial change from baseline to the 6-week assessment.

The estimated variance between therapists was small for all measures of clinical effectiveness. The intra-therapist correlation for the HoNOSCA, CDRS(t), MFQ and CGAS were 0.017, 0.005, 0.005 and 0.033, respectively. If there was no underlying therapist effect, inclusion of a random effect in the model in this way would lead to a loss of precision. *Table 7* gives the analyses of the main clinical outcome measures including the therapist effect term. For illustrative purposes the analysis without the therapist random effect is given in *Table 8*. Analysis without inclusion of a therapist effect in the model gave CIs that were slightly narrow, but this would not have altered the conclusion of the analysis.

Comparison of treatments

The estimates of the time–treatment interaction from the linear random effects model analyses are shown in *Figures 3–7* and *Table 7*. For HoNOSCA, CDRS and MFQ, negative values of the time–treatment interaction and of the pool treatment effect correspond to a beneficial effect of SSRI + CBT as compared to SSRI only. For CGAS, positive values represent benefit. The time–treatment interaction term tests for a difference in the rate of change between treatments. For all four outcomes there was no suggestion of such an interaction. Consequently, an analysis without an interaction term is justified. Without the interaction, the treatment factor in the model gives an estimate of the treatment effect averaged across the assessments, referred to here as the pooled treatment effect. Again, there was no evidence of a difference between the two treatments.

For CGI, the proportion of patients in each category was similar between treatment arms (*Table 9*). At 6 weeks 35.8% of patients were very or much improved in the SSRI only arm and 35% in the

TABLE 6 *Comparison of groups for primary and secondary outcome measures*

Outcome measure	SSRI only						SSRI + CBT					
	Mean	SD	Median	Min.	Max.	*n*	Mean	SD	Median	Min.	Max.	*n*
Primary												
HoNOSCA												
Base	25.5	5.6	26	7	42	103	25.1	5.5	25	13	40	105
6 weeks	19.2	7.6	19	3	39	98	18.7	7.0	18	2	34	98
12 weeks	18.0	7.5	18	2	35	101	17.1	8.3	17	1	39	101
28 weeks	14.5	8.3	14	1	38	95	15.4	8.6	15	0	35	98
Secondary												
CDRS(t)												
Base	75.3	6.7	76.0	58.0	86.0	103	75.1	6.7	75.0	60.0	86.0	105
6 weeks	64.6	10.1	65.0	40.0	85.0	97	65.3	9.3	64.5	42.0	86.0	98
12 weeks	61.0	11.8	62	30	84	99	62.8	12.4	62.5	37	86	100
28 weeks	55.8	12.7	56.5	30	84.5	94	57.3	13.5	58	30	86	98
CDRS (raw)												
Base	59.0	9.5	59	33	79	103	58.9	10.5	58	35	93	104
6 weeks	43.9	13.5	43	20	74	97	45.0	13.9	43	21	86	98
12 weeks	40.0	13.9	38	17	72	99	42.5	16.8	39	19	90	100
28 weeks	34.6	13.4	31.5	17	73	94	36.4	15.3	33	17	79	98
MFQ												
Base	38.2	12.7	39	7	61	103	37.9	11.9	40	6	60	105
6 weeks	25.4	13.8	26	0	54	97	25.5	13.0	24	1	53	98
12 weeks	21.6	14.8	21	0	51	99	22.7	15.4	20	0	58	100
28 weeks	15.5	15.0	11	0	60	93	18.9	15.5	11.5	0	55	98
CGAS												
Base	40.3	6.3	39	30	65	103	41.6	6.0	41	30	60	105
6 weeks	48.0	10.2	48	31	85	98	48.9	10.7	48	31	85	98
12 weeks	50.7	12.1	49.5	11	74	100	52.1	14.3	49	18	81	101
28 weeks	57.8	14.5	58.5	31	87	94	57.2	16.4	55	15	95	98

TABLE 7 *Linear random effects models analysis with CBT therapist random effect*

Outcome measure	Treatment effect[a]	95% CI	*p*-Value
Primary			
HoNOSCA			
Time–treat interaction	0.048	–0.059 to 0.155	0.37
Pooled treatment effect	0.001	–1.519 to 1.521	0.99
Secondary			
CDRS(t)			
Time–treat interaction	–0.023	–0.189 to 0.143	0.79
Pooled treatment effect	1.432	–0.709 to 3.572	0.19
MFQ			
Time–treat interaction	0.090	–0.108 to 0.287	0.37
Pooled treatment effect	1.271	–1.256 to 3.797	0.33
CGAS			
Time–treat interaction	–0.029	–0.218 to 0.160	0.76
Pooled treatment effect	0.162	–2.535 to 2.860	0.91

[a] Difference between SSRI + CBT and SSRI only adjusted for baseline value of HoNOSCA, CDRS(t score), CGAS, MFQ, age, sex, centre.

TABLE 8 *Linear random effects models analysis without the random effect for CBT therapist*

Outcome measure	Treatment effect[a]	95% CI	*p*-Value
Primary			
HoNOSCA			
Time–treat interaction	0.046	–0.046 to 0.137)	0.33
Pooled treatment effect	–0.100	–1.655 to 1.455	0.90
Secondary			
CDRS(t)			
Time–treat interaction	–0.023	–0.171 to 0.125	0.76
Pooled treatment effect	1.228	–1.099 to 3.555	0.30
MFQ			
Time–treat interaction	0.087	–0.081 to 0.256	0.31
Pooled treatment effect	1.275	–1.577 to 4.128	0.38
CGAS			
Time–treat interaction	–0.027	–0.193 to 0.138	0.75
Pooled treatment effect	0.143	–2.522 to 2.809	0.92

[a] Difference between SSRI + CBT and SSRI only adjusted for baseline value of HoNOSCA, CDRS(t score), CGAS, MFQ, age, sex, centre.

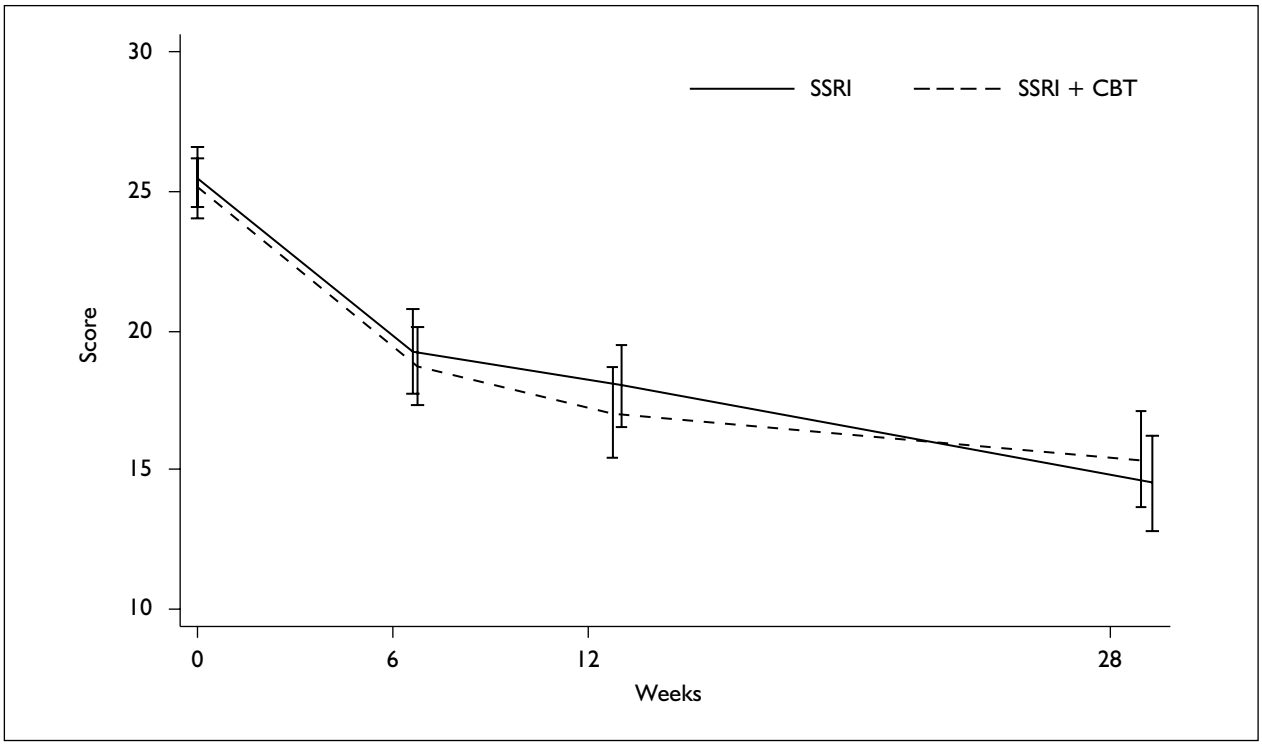

FIGURE 3 *Mean outcome by treatment group with 95% CI error bars for HoNOSCA*

SSRI + CBT arm. By 12 weeks, the proportion very or much improved had increased to 45% and 43%, respectively, but the numbers that were very or much worse increased to 12% and 11%, respectively. In *Table 9*, the effect of treatment estimated from the ordinal logistic random effects model is summarised. The common odds ratio is the odds of being in a higher (worse) CGI category for patients in the SSRI + CBT treatment arm compared with the SSRI only arm. Values <1 represent the benefit of SSRI + CBT treatment compared with the SSRI only treatment. Hence odds ratios <1 for the time–treatment interaction represent a more rapidly declining

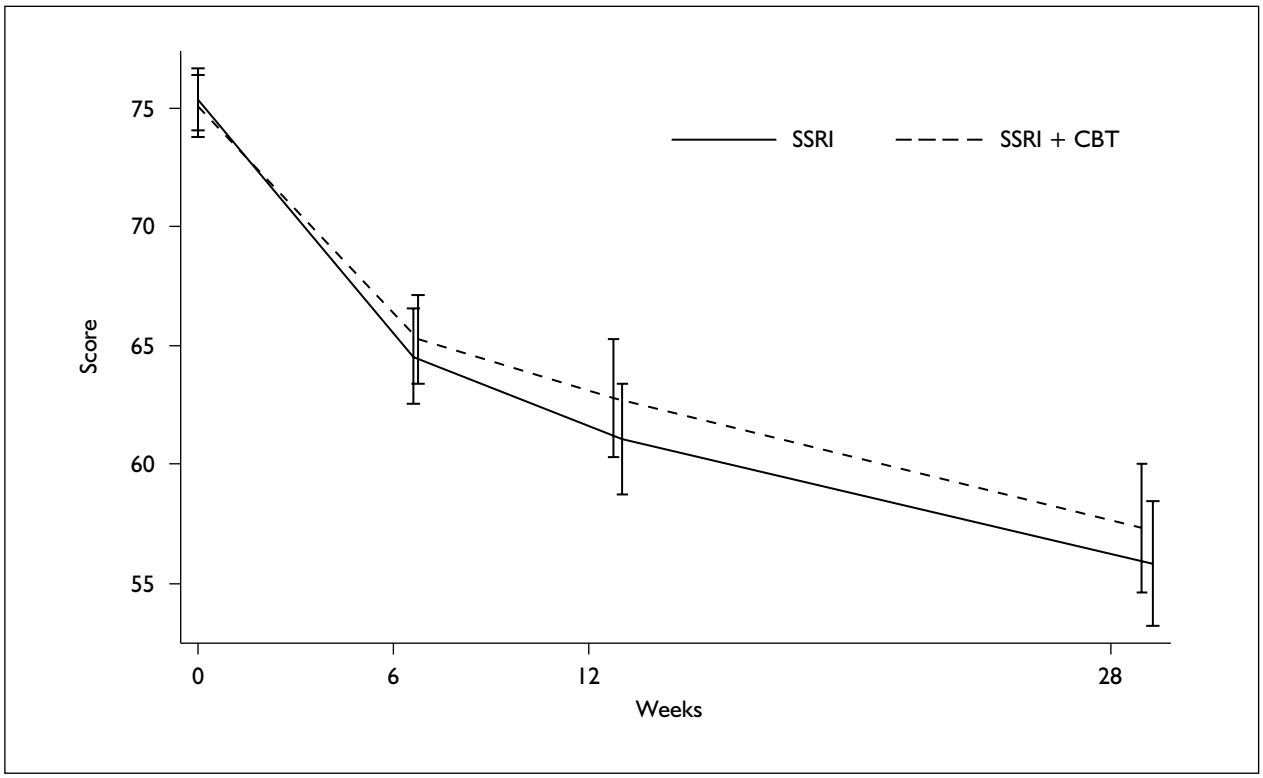

FIGURE 4 *Mean outcome by treatment group with 95% CI error bars for CDRS (t-score)*

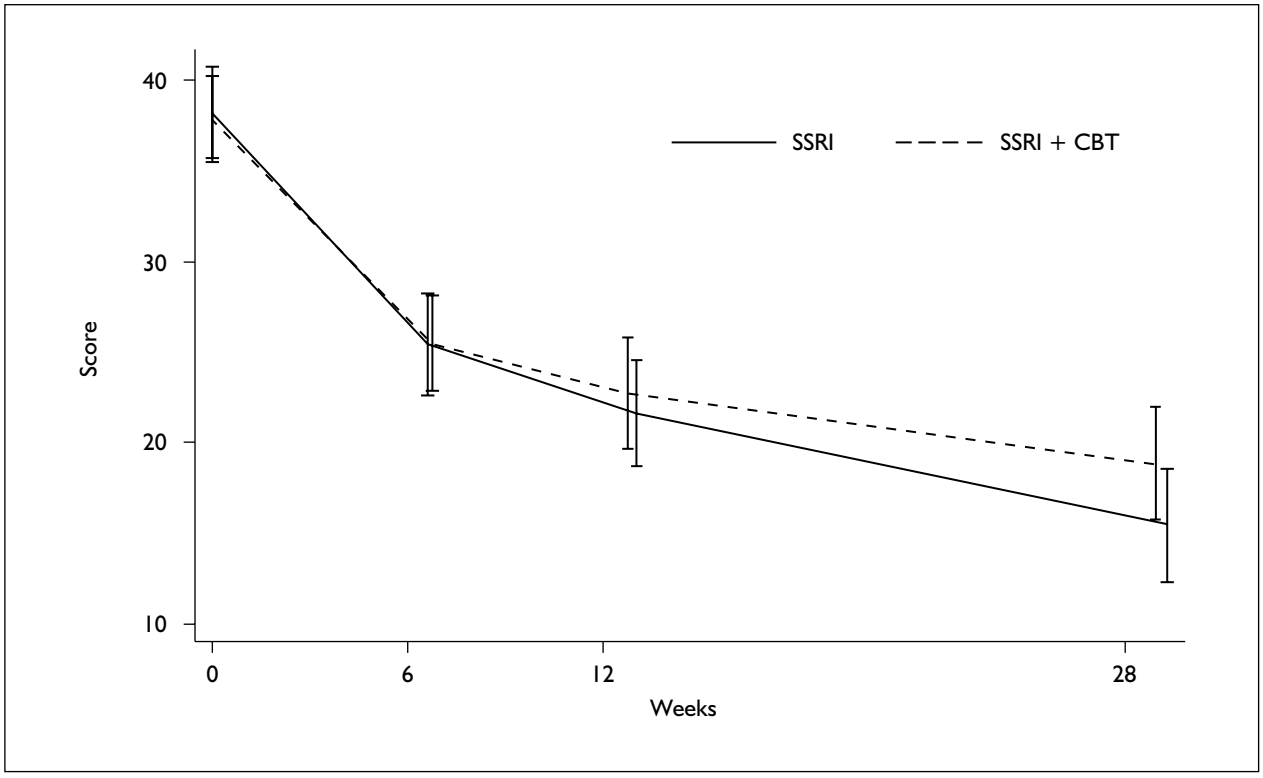

FIGURE 5 *Mean outcome by treatment group with 95% CI error bars for MFQ*

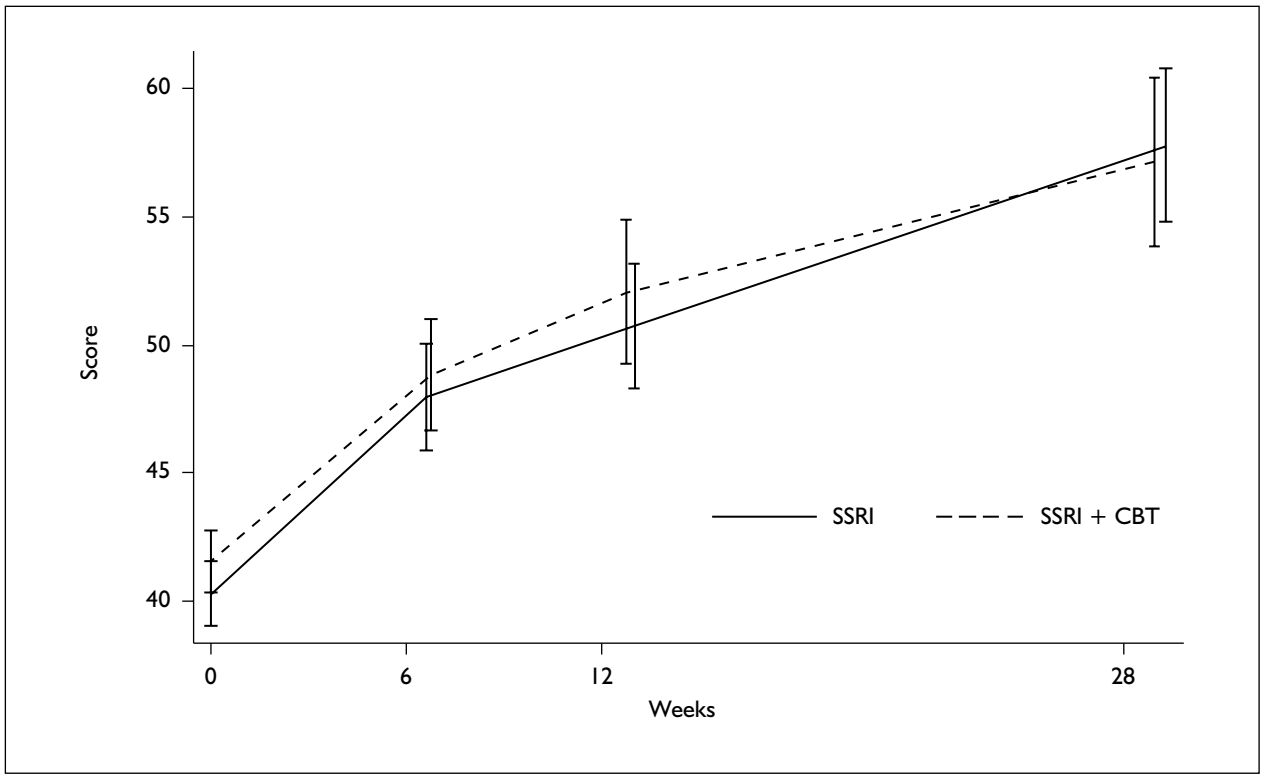

FIGURE 6 *Mean outcome by treatment group with 95% CI error bars for CGAS*

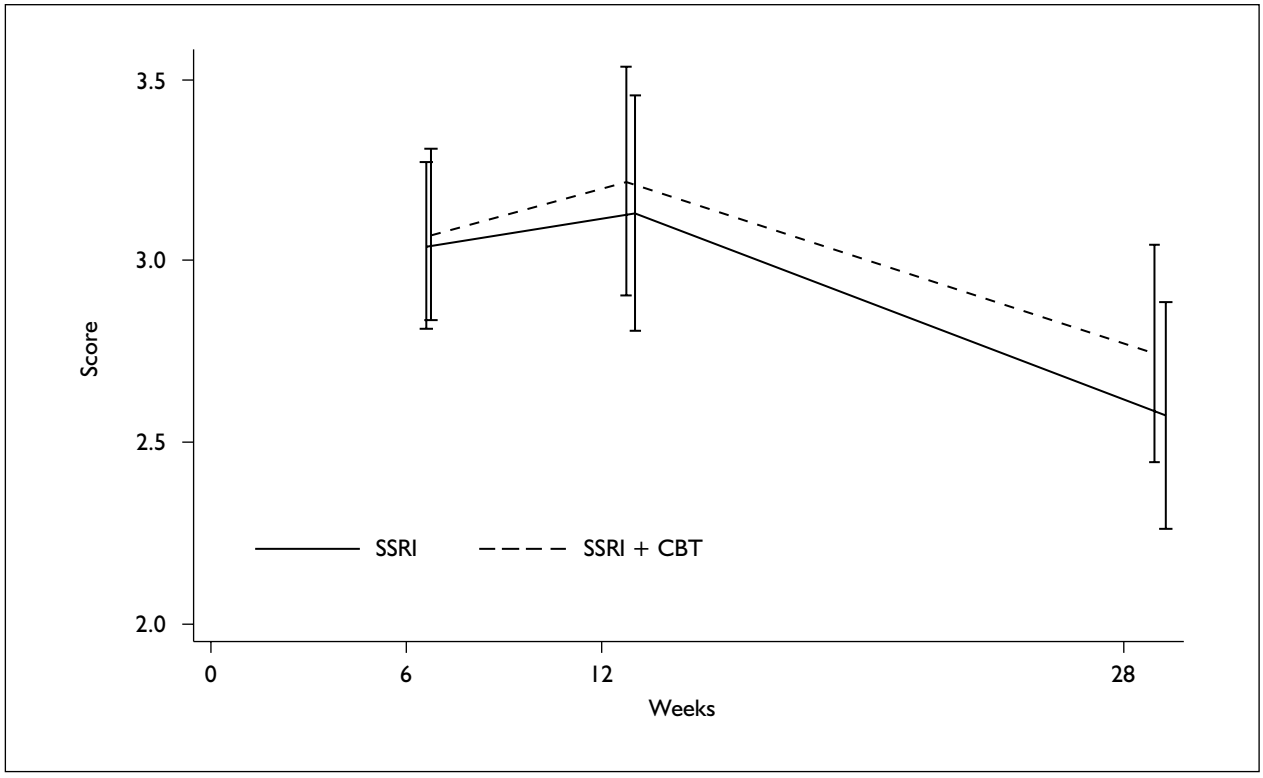

FIGURE 7 *Mean outcome by treatment group with 95% CI error bars for CGAS CGI*

TABLE 9 *CGI in words at follow-up*

	SSRI		SSRI + CBT	
	Frequency	**%**	**Frequency**	**%**
6 weeks				
Very much improved	3	3.1	1	1.0
Much improved	32	32.7	33	34.0
Minimally improved	36	36.7	37	38.1
No change	16	16.3	16	16.5
Minimally worse	8	8.2	6	6.2
Much worse	2	2.0	2	2.1
Very much worse	1	1.0	2	2.1
n	98		97	
12 weeks				
Very much improved	12	11.9	5	5.0
Much improved	32	31.7	37	36.6
Minimally improved	27	26.7	29	28.7
No change	7	6.9	9	8.9
Minimally worse	11	10.9	10	9.9
Much worse	8	7.9	4	4.0
Very much worse	4	4.0	7	6.9
n	101		101	
28 weeks				
Very much improved	20	21.3	19	19.4
Much improved	37	39.4	33	33.7
Minimally improved	21	22.3	22	22.4
No change	6	6.4	11	11.2
Minimally worse	3	3.2	7	7.1
Much worse	3	3.2	3	3.1
Very much worse	4	4.3	3	3.1
n	94		98	

Ordinal logistic random effects model analysis for CGI

	Adjusted common odds ratio	**95% CI**	***p*-Value**
Time–treat interaction[a]	1.01	0.97 to 1.05	0.672
Pooled treatment effect[a]	1.28	0.81 to 2.01	0.291

[a] Adjusted for sex, age, behavioural disorder, baseline, HoNOSCA, CDRS(t), MFQ and CGAS.

odds for the SSRI + CBT treatment arm compared with the SSRI only arm. A pooled treatment effect <1 represents a reduced odds of being in a higher category for the SSRI + CBT treatment arm. From *Table 9*, it can be seen that there is no evidence of a benefit of SSRI + CBT for CGI.

Subgroup analysis: severity and treatment

In the original analysis, a subgroup analysis was planned to investigate the relationship between severity and treatment effect. This was to be tested by including a treatment with severity (CGAS ⩽ 40) interaction term in the statistical model. In the absence of a treatment effect, such an effect is unlikely. When the interaction term was added to the model in *Table 10*, there was no significant interaction. These results are summarised in *Table 10*. For HoNOSCA, CDRS and MFQ a positive value for the interaction term represents a worse outcome for SSRI + CBT patients compared with SSRI only for patients with a lower CGAS

TABLE 10 *Treatment severity interaction term*

	Interaction	**95% CI**	***p*-Value**
HoNOSCA	0.78	–2.36 to 3.92	0.63
CDRS	2.17	–2.54 to 6.89	0.37
MFQ	2.67	–3.17 to 8.51	0.37
CGAS	–2.09	–7.44 to 3.26	0.44

score at baseline. For CGAS, a negative outcome suggests the corresponding worse outcome.

Self-harm and suicidality

Self-harm and suicidality were assessed from both HoNOSCA and the K-SADS-PL interview data.

HoNOSCA data

Table 11 summarises the frequency of responses to HoNOSCA Question 3, by treatment group and time point.

The HoNOSCA question measures a broad grouping of non-accidental self-injury methods (e.g. hitting self and self-cutting, suicide attempts, overdoses, hanging, drowning). From the ordinal logistic random effects model analyses, there is no evidence of a difference between treatments in the responses. This indicates neither an increase nor a decrease in self-injurious behaviours (with or without suicidal intent) as a consequence of being treated in either group. There is no suggestion that SSRIs increase the liability for these particular types of adverse behaviours over the treatment period.

K-SADS-PL data

Table 12 gives the frequency of participants recording clinical symptoms from K-SADS-PL by treatment group and assessment point together

TABLE 11 *Self-harm events from HoNOSCA*

	SSRI		SSRI + CBT	
	Frequency	**%**	**Frequency**	**%**
Baseline				
No problem	16	15.7	21	20.0
Occasional	21	20.6	27	25.7
Non-hazardous	24	23.5	23	21.9
Moderate	28	27.5	24	22.9
Serious	13	12.7	10	9.5
Total	102		105	
6 weeks				
No problem	46	46.9	46	46.5
Occasional	18	18.4	11	11.1
Non-hazardous	15	15.3	28	28.3
Moderate	13	13.3	9	9.1
Serious	6	6.1	5	5.1
Total	98		99	
12 weeks				
No problem	55	54.5	56	55.4
Occasional	20	19.8	15	14.9
Non-hazardous	10	9.9	16	15.8
Moderate	10	9.9	9	8.9
Serious	6	5.9	5	5.0
Total	101		101	
28 weeks				
No problem	63	66.3	62	63.3
Occasional	15	15.8	9	9.2
Non-hazardous	7	7.4	17	17.3
Moderate	4	4.2	4	4.1
Serious	6	6.3	6	6.1
Total	95		98	

Summary of ordinal logistic random effects analyses for HoNOSCA Question 3

	Adjusted common odds ratio	95% CI	*p*-Value
Time–treatment interaction[a]	1.01	0.96 to 1.06	0.595
Pooled treatment effect[a]	1.27	0.70 to 2.30	0.432

[a] Adjusted for time, sex, age, behavioural disorder at baseline, centre, HoNOSCA Question 3 score at baseline.

with the longitudinal analysis using a logistic random effects model. The numbers of symptoms reduced over time for both treatments for most outcomes so that the odds reduced over time. For the time–treatment interaction term, an odds ratio <1 would mean a more rapid improvement for SSRI + CBT compared with SSRI only. For the pooled treatment effect term, odds ratios <1 suggest suicidal acts were less likely for SSRI + CBT compared with SSRI only.

TABLE 12 *Threshold level for K-SADS-PL items related to suicidality and self-harm by treatment group and assessment*

Time (weeks)	SSRI			SSRI + CBT		
	Frequency	%	*n*	Frequency	%	*n*
Thoughts						
Baseline	48	46.6	103	50	47.6	105
6	23	23.5	98	17	17.3	98
12	17	17.0	100	19	18.8	101
28	11	11.7	94	15	15.3	98
Ideation						
Baseline	44	42.7	103	40	38.1	105
6	18	18.4	98	10	10.2	98
12	13	13.0	100	16	15.8	101
28	9	9.6	94	13	13.3	98
Acts						
Baseline	21	20.4	103	13	12.4	105
6	9	9.2	98	5	5.1	98
12	8	8.0	100	7	6.9	101
28	6	6.4	94	7	7.1	98
Medical lethality						
Baseline	4	3.9	103	3	2.9	105
6	1	1.0	98	2	2.0	98
12	1	1.0	100	3	3.0	101
28	2	2.1	94	3	3.1	98
Self-harm (non-suicidal)						
Baseline	23	22.3	103	30	28.6	105
6	5	5.1	98	18	18.4	98
12	11	11.0	100	15	14.9	101
28	9	9.6	94	12	12.2	98

	Odds ratio[a,b]	95% CI	*p*-Value
Thoughts			
Time–treatment interaction	1.020	0.96 to 1.08	0.525
Pooled treatment effect	0.855	0.38 to 1.91	0.702
Ideation			
Time–treatment interaction	1.039	0.97 to 1.11	0.243
Pooled treatment effect	0.917	0.40 to 2.10	0.837
Acts			
Time–treatment interaction	1.002	0.93 to 1.08	0.955
Pooled treatment effect	0.995	0.45 to 2.21	0.99
Medical lethality			
Time–treatment interaction	0.947	0.86 to 1.05	0.285
Pooled treatment effect	1.572	0.58 to 4.27	0.375
Self-harm (non-suicidal)			
Time–treatment interaction	0.935	0.88 to 1.00	0.046
Mid-point treatment effect	2.280	1.01 to 5.14	0.047

[a] Adjusted for time, sex, age, behavioural disorder at baseline, centre and baseline value.
[b] From the model with a time–treatment interaction with a centred time variable.

There is no evidence of a difference between treatments for level of suicidal thoughts. For non-suicidal self-harm there is an interaction between treatment and time ($p = 0.046$). Inspection of the frequencies shows that few subjects in the SSRI only group reported threshold levels of the self-harm at the 6-week assessment. Where there is a significant interaction, interpretation of the main effects in a statistical model is more complex. The time variable was centred so that the pooled treatment effect represents the effect at the mid-point.

Adverse events and side-effects

The frequency and characteristics of adverse events are shown in *Tables 13* and *14*.

Attendance, compliance and quality of treatment

Table 15 gives the frequency distribution of the number of sessions attended by patients in each treatment arm. *Table 16* give the distribution of sessions for CBT. By 12 weeks, 89% (93/105) of patients in the SSRI + CBT arm had received four or more sessions including CBT. By 28 weeks, this increased slightly to 93% (97/105).

There was evidence that compared with other therapists, psychiatrists had a lower median quality score ($p = 0.0005$) (*Table 16*) and a lower mean quality score (mean difference = –9.6, 95% CI –14.5 to –4.6, $p = 0.0002$). To investigate whether baseline characteristics might be confounding variables for therapists, a regression model including therapist, type, sex and age of patient, behavioural disorder, centre (Manchester/Cambridge) and baseline values of CDRS(t), HoNOSCA, MFQ and CGAS was used. This did not change the magnitude of the difference between psychiatrist and CBT therapist. Nevertheless, patients with a higher CGAS score at baseline received slightly better CBT ($p = 0.022$).

Table 17 gives the quality of CBT by type of therapist. To examine whether quality of CBT influenced outcome, a longitudinal regression model was fitted to those patients with a quality score including the same baseline covariates as the main analysis of outcome. *Table 18* summarises the estimate of the effect of quality on outcome. Although the coefficient was negative, suggesting that outcome improved as quality score increased, this was not a statistically significant effect. A 10-point increase in the quality score, the approximate difference between CBT therapists and psychiatrist, corresponded to an approximately half-point reduction in HoNOSCA

TABLE 13 *Adverse events*

	SSRI		SSRI + CBT	
	Frequency	**%**	**Frequency**	**%**
No. of events	185		175	
No. of patients with event recorded	61	59.2	65	61.9
Serious events	4	2.2	2	1.1
Intensity				
Mild	156	84.3	145	82.9
Moderate	28	15.1	27	15.4
Severe	1	0.5	3	1.7
Related				
Related	93	50.3	60	34.3
Possibly related?	67	36.2	72	41.1
Probably related?	23	12.4	42	24.0
Unrelated	2	1.1	1	0.6
Action				
None	169	91.4	157	89.7
Dose decreased	4	2.2	4	2.3
Dose increased	1	0.5	1	0.6
Drug stopped	8	4.3	10	5.7
Time changed	2	1.1	0	0.0
Not known	1	0.5	3	1.7

TABLE 14 *Category of adverse events recorded*

Category	SSRI		SSRI + CBT		Total	
	Frequency	%	Frequency	%	Frequency	%
Lower blood pressure	0	0.0	1	0.6	1	0.3
Headaches	25	13.5	19	10.9	44	12.2
Nausea	23	12.4	15	8.6	38	10.6
Reduced appetite	11	5.9	17	9.7	28	7.8
Insomnia	5	2.7	7	4.0	12	3.3
Loose stools	2	1.1	4	2.3	6	1.7
Shaking	4	2.2	5	2.9	9	2.5
Tiredness	19	10.3	23	13.1	42	11.7
Increased appetite	1	0.5	0	0.0	1	0.3
Blurred vision	5	2.7	4	2.3	9	2.5
Creeping feeling	2	1.1	0	0.0	2	0.6
Muscle twitches	8	4.3	6	3.4	14	3.9
Shooting pains	2	1.1	7	4.0	9	2.5
Poor concentration	3	1.6	2	1.1	5	1.4
Nightmares	1	0.5	5	2.9	6	1.7
Fainting	6	3.2	6	3.4	12	3.3
Flatulence	0	0.0	2	1.1	2	0.6
Rash	2	1.1	1	0.6	3	0.8
Restless	15	8.1	9	5.1	24	6.7
Dry mouth	15	8.1	13	7.4	28	7.8
Tics	0	0.0	2	1.1	2	0.6
Stomach pains	4	2.2	3	1.7	7	1.9
Drowsy	4	2.2	2	1.1	6	1.7
Dizzy	6	3.2	5	2.9	11	3.1
Increased weight	1	0.5	1	0.6	2	0.6
Indigestion	0	0.0	1	0.6	1	0.3
Poor memory	0	0.0	1	0.6	1	0.3
Disinhibition	0	0.0	1	0.6	1	0.3
Overactive	1	0.5	0	0.0	1	0.3
Irritability	5	2.7	2	1.1	7	1.9
Disorientation	1	0.5	0	0.0	1	0.3
Hotness	1	0.5	0	0.0	1	0.3
Clammy hands	1	0.5	0	0.0	1	0.3
Clumsy	1	0.5	0	0.0	1	0.3
Panicky feelings	0	0.0	1	0.6	1	0.3
Reduced weight	0	0.0	1	0.6	1	0.3
Early morning waking	1	0.5	0	0.0	1	0.3
Heartburn	1	0.5	0	0.0	1	0.3
Derealisation	2	1.1	1	0.6	3	0.8
Low mood	1	0.5	1	0.6	2	0.6
Agitated	1	0.5	0	0.0	1	0.3
Spaced out	1	0.5	0	0.0	1	0.3
Generalised seizures	2	1.1	0	0.0	2	0.6
Sweating	1	0.5	0	0.0	1	0.3
Burning sensation in skin	0	0.0	1	0.6	1	0.3
Enuresis	0	0.0	1	0.6	1	0.3
Hypomania	0	0.0	2	1.1	2	0.6
Allergy	0	0.0	1	0.6	1	0.3
Overdose[a]	1	0.5	0	0.0	1	0.3
Total	185		173		358	

[a] Adverse effects of SSRI overdose: in 18 patients, the side-effects, although not severe, resulted in a change of the medication.

TABLE 15 *Attendance at treatment sessions: frequency (%)*

No. of sessions	0–12 weeks[a]		0–28 weeks[b]		13–28 weeks[c]	
	SSRI (*n* = 103)	SSRI + CBT (*n* = 105)	SSRI (*n* = 103)	SSRI + CBT (*n* = 105)	SSRI (*n* = 103)	SSRI + CBT (*n* = 105)
0	5 (4.9)	0	4 (3.9)	0	27 (26.2)	24 (22.9)
1	10 (9.7)	3 (2.9)	8 (7.8)	1 (1.0)	17 (16.5)	13 (12.4)
2	11 (10.7)	5 (4.8)	6 (5.8)	5 (4.8)	14 (13.6)	14 (13.3)
3	16 (15.5)	4 (3.8)	11 (10.7)	3 (2.9)	15 (14.6)	11 (10.5)
4	19 (18.4)	10 (9.5)	7 (6.8)	4 (3.8)	12 (11.7)	7 (6.7)
5	12 (11.7)	13 (12.4)	7 (6.8)	12 (11.4)	8 (7.8)	11 (10.5)
6	20 (19.4)	17 (16.2)	12 (11.7)	3 (2.9)	5 (4.9)	6 (5.7)
7	5 (4.9)	7 (6.7)	5 (4.9)	8 (7.6)	2 (1.9)	7 (6.7)
8	1 (1.0)	12 (11.4)	14 (13.6)	7 (6.7)	2 (1.9)	2 (1.9)
9	2 (1.9)	10 (9.5)	8 (7.8)	7 (6.7)	1 (1.0)	4 (3.8)
10	1 (1.0)	7 (6.7)	7 (6.8)	4 (3.8)		3 (2.9)
11	1 (1.0)	3 (2.9)	3 (2.9)	6 (5.7)		1 (1.0)
12		2 (1.9)	4 (3.9)	9 (8.6)		1 (1.0)
13		8 (7.6)	3 (2.9)	6 (5.7)		0
14		3 (2.9)	0	4 (3.8)		1 (1.0)
15		0	1 (1.0)	4 (3.8)		
16		0	1 (1.0)	2 (1.9)		
17		0	1 (1.0)	7 (6.7)		
18		0	0	1 (1.0)		
19		1 (1.0)	0	4 (3.8)		
20			1 (1.0)	2 (1.9)		
21				2 (1.9)		
22				1 (1.0)		
23				1 (1.0)		
25				1 (1.0)		
26				1 (1.0)		
Mean (SD)	4.1 (2.3)	7.2 (3.5)	6.5 (4.0)	10.6 (5.7)	2.4 (2.2)	3.4 (3.2)
Median	4.0	7.0	6.0	5.0	2.0	3.0

[a] Mann–Whitney *U* test, 2439.00, Z –6.88, $p < 0.001$ at 12 weeks.
[b] Mann–Whitney *U* test, 3081.00, Z –5.37, $p < 0.001$ for 28 weeks.
[c] Mann–Whitney *U* test, 4567.00, Z –1.96, $p = 0.050$ for sessions after 12 weeks.

TABLE 16 *Numbers of sessions of CBT (frequency distribution) for the SSRI + CBT group* (n = *105)*

Sessions	0–12 weeks		13–28 weeks		Total	
	Frequency	%	Frequency	%	Frequency	%
0	5	4.8	28	26.7	2	1.9
1	6	5.7	13	12.4	3	2.9
2	1	1.0	15	14.3	5	4.8
3	5	4.8	12	11.4	4	3.8
4	16	15.2	7	6.7	8	7.6
5	11	10.5	8	7.6	9	8.6
6	16	15.2	3	2.9	5	4.8
7	6	5.7	9	8.6	7	6.7
8	12	11.4	3	2.9	9	8.6
9	13	12.4	2	1.9	5	4.8
10	4	3.8	2	1.9	5	4.8
11	2	1.9	1	1.0	6	5.7
12	3	2.9		0.0	10	9.5
>12	4		1	1.0	26	24.8

TABLE 17 *Quality of CBT by type of operator*

Therapist	Mean	SD	Median	Min.	Max.	*N*
Psychiatrist	54.7	10.5	55.5	29	76	64
CBT therapist	64.2	8.8	66.0	35	73	22
Total	57.1	10.9	59.0	29	76	86

TABLE 18 *Comparison of outcome taking account of quality score*

	Coefficient of quality score[a]	95% CI	*p*-Value
HoNOSCA	–0.054	–0.178 to 0.070	0.393
CDRS(t)	–0.082	–0.266 to 0.101	0.379
MFQ	–0.058	–0.281 to 0.165	0.611
CGAS	0.142	–0.066 to 0.350	0.182

[a] Adjusted for baseline covariates: sex, age, behavioural disorder, centre, baseline, HoNOSCA, CDRS(t).

and a 0.8 reduction in the CDRS (*t*-score). This analysis assumes that the quality score for a single session was indicative of the quality of other sessions so that any effect of quality will tend to be attenuated. What is more, some patients received treatment from more than one therapist.

Summary of clinical trial

Characteristics of the sample

The study sample was a post-pubertal adolescent population recruited exclusively from referrals to CAMHS services through standard primary care procedures via GPs. The population was predominantly white European. As would be expected from recent UK epidemiological findings,[3] there was a female:male sex ratio of 3:1 and half of the families had an absent biological parent.

A striking feature is the severity of illness. Unlike almost all other reported trials, the majority of this sample has a severe illness with markedly high levels of psychosocial impairment and a high number of depressive symptoms. As expected for a severely ill group, over 80% of patients had concurrent non-depressive co-morbid disorders at first assessment. Social phobia and obsessive–compulsive disorder was the most common. Disruptive behaviour disorders were not particularly common and developmental disorders were uncommon. Surprisingly, despite the severity of the presenting illness, chronic depressive states (dysthymic conditions) lasting more than 1 year were rare.

This study was also unusual as it included high-risk suicidality, which has usually been excluded from such trials. Half of participants had engaged in a suicidal act in the past, and nearly one-quarter of these occurred in the month prior to randomisation. One-third had repeatedly self-harmed.

A further unusual feature of this trial was that cases of mood-congruent psychosis were also included (16 in total, 8%). Therefore, the sample recruited probably represents the most suicidal and impaired group of depressed adolescents yet studied in an RCT, representative of CAMHS NHS populations.

Treatment pathway

The trial focused on depressed patients who were not remitting at the time of referral, to prevent the inclusion of those already likely to improve or recover in the next few weeks. This was achieved by offering a psychoeducational BII to those who had not already had such a procedure prior to randomisation. If clinically severe, such a procedure was not offered and patients went straight to randomisation. It is striking that around one-fifth of depressed patients responded to BII and did not proceed to randomisation. The nature and characteristics of these responders were not assessed and it is not possible to delineate the characteristics that may distinguish BII responders from non-responders.

The numbers of withdrawals from the study following randomisation were minimal and 204 (98%) of the study participants had data at one or

more assessment points over the 28 weeks. Primary end-point data (at 12 weeks) were available on 202 (97%) subjects. Six-week data were available on three of the withdrawn subjects. At 28 weeks, 15 research assessments were not completed. Overall, only four cases (2%) did not complete any assessments after baseline, resulting in 204 (98%) participants with at least one research assessment post-baseline.

The most common reason for treatment withdrawal prior to the 12-week primary end-point was that families wanted a change of treatment (nine cases: five SSRI + CBT, four SSRI only) and in one case the patient improved. A further seven cases were clinician-initiated withdrawals as a result of deteriorating illness, possible adverse effects or a protocol violation. Overall, there continued to be a small number of further withdrawals (n = 14) over the 28-week trial period. Eight of these were for deterioration (two SSRI + CBT, six SSRI only), four were for improvement (three SSRI + CBT, one SSRI only), one case in the SSRI + CBT arm did not want further treatment and one participant moved (SSRI + CBT). In total, 31 (15%) of the study sample formally withdrew from treatment before the end of the study.

Comparison of treatments

There was no support for the primary hypothesis that SSRI + CBT would have a significantly better outcome by 28 weeks than SSRI only treatment. There was no difference in the HoNOSCA scores between the two treatment arms at any point over the 28-week study period. Further analyses using the secondary outcome measures also show that there is no significant advantage for SSRI + CBT over SSRI only treatment. Levels of self- and respondent-measured depressive symptoms were no different between the two groups at any point over the 28-week period. This is not due to non-response to treatment since both arms showed an equivalent degree of improvement over time. Controlling for potential influences that might accrue from a variety of baseline characteristics does not alter the findings of the main analyses. All patients in both arms continued to receive ACC throughout the trial, as would be expected in routine NHS settings. Therefore, the study cannot determine if SSRI, specifically fluoxetine, is effective in the absence of ACC.

Responders and non-responders

Clinical global evaluation throughout the treatment period revealed a substantial number of patients who do not respond to SSRI only or SSRI + CBT. The increasing number of responders between 12 and 28 weeks is on average increased compared with 6–12 weeks. This suggests a differential degree of sensitivity to the treatment. Although the majority will show a level of response by 6 weeks (around 70%) as expected, perhaps a further 10–20% will show delayed response not evident until between 12 and 28 weeks from the start of treatment. The proportion of non-responders (taken as all those who are rated as no change through to very much worse) by 28 weeks is 20.8%. Since it is different subjects reporting poor response at different time points, it may be that some individuals are truly non-responsive throughout the trial, others are poorly compliant and a further group reflect an undulating non-linear response to treatment even when compliant. Overall, perhaps around 10% of the trial population are truly treatment resistant.

Self-harm and suicide

The population recruited for this treatment were at high suicidal risk on first assessment. There is no increase in the reports of self-harm, suicidal ideation or action in either treatment arm. Inspection of the data shows that between 15% and 20% of the patients report no problems with these symptoms at baseline. By 6 weeks, this proportion (reporting no problems) has risen in both arms to 45% and continues to rise to over two-thirds in each group by the 28-week assessment. There is no evidence that SSRIs with or without CBT are likely to result in a significant increase in self-harm or suicide over the treatment period. Treatment is associated with a modest but significant decrease in non-suicidal self-harm by 6 weeks in the SSRI only arm.

Side-effects and adverse events

The number of patients with side-effects reported was around two-thirds. The majority (>90%) of reported events were considered clinically to be related or possibly/probably related to treatment. Among these, <1% were considered severe. Of these, only 1–2% were rated as serious and required a change in treatment. One adverse event was described as 'serious', where an adolescent had a fit and medication could not be excluded as a possible cause. Overall, no action was required for 90% of the reported events and side-effects. In 18 (10%) of the patients, the side-effects, although not severe, resulted in the medication being stopped. The commonest adverse events and/or side-effects reported were headaches, nausea, tiredness, dry mouth and reduced appetite. Irritability was reported in around 2% and

disinhibition in <0.5%. There were no differences between the two treatment arms in either the number of events reported or the proportion of patients who reported them. There is no evidence that the addition of CBT decreases the liability for reporting either the number or the type of side-effects over the trial period.

Attendance, compliance and quality of treatment

Although patients in Cambridge are more likely to attend treatment sessions over the trial period, this did not influence the overall outcome or differences between the groups by 28 weeks. This suggests that the minimum number of attendances for therapeutic benefit in the short term may be lower than currently assumed in patients with moderate to severe depression.

Overall attendance in the SSRI + CBT arm did not reflect the amount of treatment that was available (19 sessions or more). By 28 weeks, the mean attendance in this arm was 11 sessions. However, 91% of participants attended a minimum of four sessions, with only 9% attending fewer than this. Reasons for treatment withdrawal in the SSRI + CBT arm were deterioration (six), improvement (four), family did not want treatment or wanted a change in treatment (eight), adverse effects of medication (one) and relocation (one). These subjects would therefore have attended fewer sessions. The level of attendance in this study reflects the difficulties of engaging with such an impaired population and is probably greater than would normally be achieved in the NHS, in view of the fact that the research team endeavoured to retain participants as much as possible, over and above the efforts that would normally be made in a busy NHS clinic.

Despite the greater mean attendance in the SSRI + CBT arm compared with the SSRI only arm, there were no significant differences in outcomes.

The findings show that CBT is generally well delivered by all therapists, despite the differences in training. Where therapist scores fell below the level for adequate treatment, in six of these seven cases patients were rated as uncooperative with treatment. Fully trained CBT therapists are somewhat more likely to deliver CBT closer to the expected 'gold standard', although this has no influence on the liability for improvement within the SSRI + CBT arm. There is also evidence that level of impairment influences the quality of CBT. Thus less impaired patients at entry received better CBT treatment regardless of therapist type. This is consistent with the literature that CBT is likely to be effective in moderate and mild depressive disorders.[76]

Economic evaluation

Full economic data were available for 188 young people (90%), 96 in the SSRI + CBT group and 92 in the SSRI only group. A comparison of baseline characteristics revealed a significant centre difference between those included in the economic evaluation and those who were missing, with 95% of missing data coming from Manchester ($p = 0.015$) (*Table 19*). No other significant differences were found and there was no difference overall in missing data between the two treatment groups. Length of follow-up varied greatly (range 21–51 weeks); however, there was no significant difference in length of follow-up between the two treatment groups on average (mean 29 weeks in both groups). There was also no significant

TABLE 19 *Comparison of baseline characteristics for patients with missing or full economic data*

Baseline variable	Available ($n = 188$)	Missing ($n = 20$)
Age in years, mean (SD)	14 (1)	14 (1)
Female (%)	72	90
Manchester (%)[a]	69	95
HoNOSCA score, mean (SD)	25 (6)	25 (5)
CGAS score, mean (SD)	41 (7)	40 (8)
Co-morbid behavioural disorder (%)	28	40
SSRI + CBT (%)	52	45
Total cost in previous 6 months, mean (SD) (£)	3062 (2181)	3175 (1868)

[a] $p < 0.05$.

TABLE 20 *EQ-5D results by treatment group*

		Mean (SD)		Difference (95% CI)[a]	*p*-Value[a]
		SSRI + CBT	SSRI only		
EQ-5D	Baseline	0.49 (0.30)	0.50 (0.29)		
	12 weeks	0.68 (0.30)	0.73 (0.25)		
	28 weeks	0.74 (0.30)	0.78 (0.26)		
QALYs	28 weeks	0.39 (0.15)	0.42 (0.13)	–0.029 (–0.08 to 0.01)	0.119

[a] Adjusted for gender, age, centre and baseline, HoNOSCA, CGAS, co-morbid behaviour disorder and EQ-5D.

difference in baseline characteristics between the two treatment groups, including total baseline costs per patient (SSRI+ CBT £2977, SSRI only £3169; $p = 0.524$).

Outcomes

The two treatment groups did not differ significantly on the primary outcome measure, the HoNOSCA, as reported above. Results for the EQ-5D are reported in *Table 20*. EQ-5D utilities show improvements in health status over time in both groups, but there is little difference between the two groups at final follow-up. Gains in QALYs are small as a result of the short timescales involved. Again, there are no significant differences between the two treatment groups.

Resource use

Table 21 details the mean number of contacts that young people had with all services over the 28-week follow-up. Resource use differed little between the two groups of young people, except for inpatient services, with the SSRI + CBT group spending more time in hospital than the SSRI only group.

Costs

Table 22 details the total costs over the 28-week follow-up. Results from the non-parametric bootstrap replications did not differ substantially from the parametric results and are not reported here. Total costs per SSRI + CBT patient were £6940, £2300 more than in the SSRI only group. This difference was not statistically significant at the 5% level of significance, but came close ($p = 0.057$). The SSRI + CBT group were significantly more expensive than the SSRI only group in terms of intervention sessions and secondary healthcare services. The difference for intervention sessions was due to the greater length of these sessions and higher attendance rates in the SSRI + CBT arm. The latter difference was due primarily to two individuals in the SSRI + CBT group who were admitted to hospital for a significant proportion of their time in the trial (65% and 92%, respectively). Overall healthcare costs were significantly higher in the SSRI + CBT group. Differences between the two groups were almost entirely due to differences in the cost of admissions. In subgroup analyses, there were no statistically significant differences in the estimated effect of SSRI + CBT on the total cost by centre (test of interaction, $p = 0.412$) or severity of illness ($p = 0.971$).

Table 23 reports the change in costs over time. Mean costs per week at baseline were very similar between the two groups. At the 12-week follow-up, the SSRI + CBT group was significantly more expensive. The SSRI + CBT group remained more expensive at the 28-week follow-up but the difference was no longer significant.

Sensitivity analysis

A number of one-way sensitivity analyses were undertaken:

1. The cost of intervention sessions was based on the salaries of the professionals involved. Since the seniority of the therapists may have been influenced by the research, these costs were recalculated to reflect likely clinical practice using the following professionals: specialist registrar, clinical psychologist grade A and mental health nurse grade F/G.
2. The main analysis excluded 'did not attends' (DNAs), which assumes that the therapist was able to use the time for alternative productive work. This assumption was removed and the full cost of a DNA included (equivalent to the cost of an attended session).
3. Estimates of the cost of supervisors' time was added on the basis of the following assumptions: (a) supervision provided by a consultant psychiatrist, (b) average of 10 intervention sessions per week, (c) average of 60 minutes of supervision per week and (d) average of 6 minutes of supervision per session per week.

TABLE 21 *Use of resources by young people during the 28-week follow-up period: mean per patient*

Service	Use of resources, mean (SD)		% using service
	SSRI + CBT (*n* = 96)	**SSRI only (*n* = 92)**	
Intervention sessions	11.3 (5.8)	7.0 (4.0)	98
Hospital services for all reasons			
Inpatient days	5.8 (24.0)	0.6 (2.7)	13
Outpatient contacts	2.1 (4.6)	1.7 (3.3)	38
Day patient contacts	0.1 (0.3)	0.0 (0.2)	3
Accident and emergency	0.5 (1.0)	0.4 (0.8)	31
Community health services			
GP contacts	2.9 (4.6)	2.6 (5.7)	91
Practice nurse contacts	0.3 (0.7)	0.5 (1.7)	30
Counsellor contacts	0.1 (0.5)	0.4 (1.9)	9
District nurse contacts	0.0 (0.1)	0.1 (0.3)	3
Community psychiatric nurse contacts	0.3 (1.6)	0.2 (1.6)	3
Community psychologist contacts	0.1 (0.4)	0.1 (0.7)	2
Group therapy contacts	0.0 (0.0)	0.2 (1.4)	2
Education			
Mainstream school weeks	16.4 (12.4)	15.2 (12.2)	74
Hospital school weeks	2.1 (5.8)	1.7 (5.4)	12
Classroom support weeks	0.6 (2.8)	1.2 (4.4)	11
Home tuition weeks	1.1 (4.4)	1.3 (4.0)	12
Exclusion service weeks	0.4 (3.0)	0.3 (2.1)	2
Education welfare officer contacts	0.1 (0.6)	0.1 (0.6)	3
Education psychologist contacts	0.0 (0.0)	0.2 (1.3)	3
School doctor contacts	0.1 (0.3)	0.0 (0.2)	2
School nurse contacts	0.7 (3.4)	0.4 (1.4)	15
Social services			
Social worker contacts	0.2 (1.0)	0.6 (2.6)	16
Family support worker contacts	0.1 (1.2)	0.0 (0.1)	1
Youth worker contacts	0.2 (1.5)	0.0 (0.0)	1
Voluntary sector services	0.2 (1.1)	0.5 (2.2)	8
Private sector services	0.2 (1.7)	0.0 (0.1)	1

TABLE 22 *Total service cost per young person over the 28-week follow-up period (£)*

	Mean (SD)		Mean difference[a] (95% CI)	*p*-Value[a]
	SSRI + CBT (*n* = 96)	**SSRI only (*n* = 92)**		
Health services	3512 (9425)	919 (1150)	2511 (568 to 4453)	
Intervention sessions	752 (683)	262 (196)	491 (344 to 639)	
Hospital services	2652 (9388)	551 (1109)	2017 (83 to 3950)	
Community health services	68 (96)	74 (126)	–9 (–41 to 22)	
Medication	40 (50)	32 (47)	9 (–5 to 23)	
Education	3400 (3556)	3575 (4089)	–55 (–1104 to 994)	
Social services	16 (70)	133 (1154)	–112 (–349 to 125)	
Voluntary sector services	6 (33)	14 (69)	–10 (–24 to 4)	
Private sector services	7 (55)	0 (3)	7 (–4 to 19)	
Total costs	6940 (11122)	4640 (4516)	2340 (–91 to 4772)	0.059
Total costs per week	244 (403)	161 (155)	85 (–3 to 173)	0.057

[a] Adjusted for gender, age, centre, baseline, HoNOSCA, CGAS, co-morbid behaviour disorder and costs.

TABLE 23 *Change in young people's costs over time; mean per week (£)*

	Mean (SD)		Mean difference[a] (95% CI)	*p*-Value[a]
	SSRI + CBT (*n* = 96)	SSRI only (*n* = 92)		
Baseline	115 (84)	121 (84)	–6 (–30 to 18)	0.573
12-week follow-up	224 (357)	134 (127)	91 (13 to 167)	0.011
28-week follow-up	244 (403)	161 (155)	85 (–3 to 173)	0.057

[a] Adjusted for gender, age, centre, baseline, HoNOSCA, CGAS, co-morbid behaviour disorder and costs.

4. The impact of the two high-cost individuals who spent the majority of the trial in hospital was explored by excluding these individuals from the analysis.
5. Travel and productivity losses borne by parents were added to provide a broader cost perspective.
6. Local costs were changed to national unit costs[52] to assess generalisability to the wider UK population.

The majority of these analyses did not alter the finding of no significant difference in cost between the two groups (*Table 24*). Inclusion of DNAs and supervisors' time increased the difference in cost between the two groups to the extent that the SSRI + CBT group became significantly more expensive than the SSRI group ($p = 0.049$ in both analyses). The removal of the two high-cost individuals greatly reduced the difference in cost ($p = 0.202$).

Cost-effectiveness analysis

Using the bootstrapped means, the SSRI + CBT group cost £2327 more than the SSRI only group and HoNOSCA scores were 0.81 points worse over 28 weeks, giving an ICER of £2873 per unit increase in HoNOSCA score, where higher scores indicate worse outcomes. Thus spending additional funds on SSRI + CBT is associated with poorer outcomes. In other words, the SSRI + CBT group is dominated by the SSRI only group, in terms of cost-effectiveness. *Figure 8* presents a scatterplot of the bootstrapped replications for incremental cost and incremental HoNOSCA score. Because poorer outcomes on the HoNOSCA are associated with higher scores, moving from left to right on the *x*-axis means a worsening in the incremental effectiveness for the SSRI + CBT group compared with the SSRI only group. The scatter plot demonstrates that SSRI + CBT is more expensive than SSRI for almost all replications (points above the *x*-axis) and is

TABLE 24 *Sensitivity analysis of 28-week cost per patient (£)*

	Mean (SD)		Mean difference[a] (95% CI)	*p*-Value[a]
	SSRI + CBT (*n* = 96)	SSRI only (*n* = 92)		
Main analysis	6,940 (11,122)	4,640 (4,516)	2,340 (–91 to 4,772)	0.059
Varying grade/profession of therapists to reflect clinical practice	6,614 (11,074)	4,531 (4,499)	2,126 (–294 to 4,546)	0.085
Including the full cost of DNAs	7,131 (11,089)	4,736 (4,516)	2,436 (10 to 4,862)	0.049
Including estimates of cost of supervisors' time	7,200 (11,119)	4,799 (4,525)	2,444 (14 to 4,874)	0.049
Excluding high-cost individuals	5,531 (5,180)	4,640 (4,516)	890 (–517 to 2,297)	0.202
Including travel costs and parental productivity losses	7,129 (11,347)	4,836 (5,171)	2,357 (–178 to 4,892)	0.068
Applying national unit costs	6,981 (11,198)	4,630 (4,502)	2,376 (–63 to 4,815)	0.056

[a] Adjusted for gender, age, centre, baseline, HoNOSCA, CGAS, co-morbid behaviour disorder and costs.

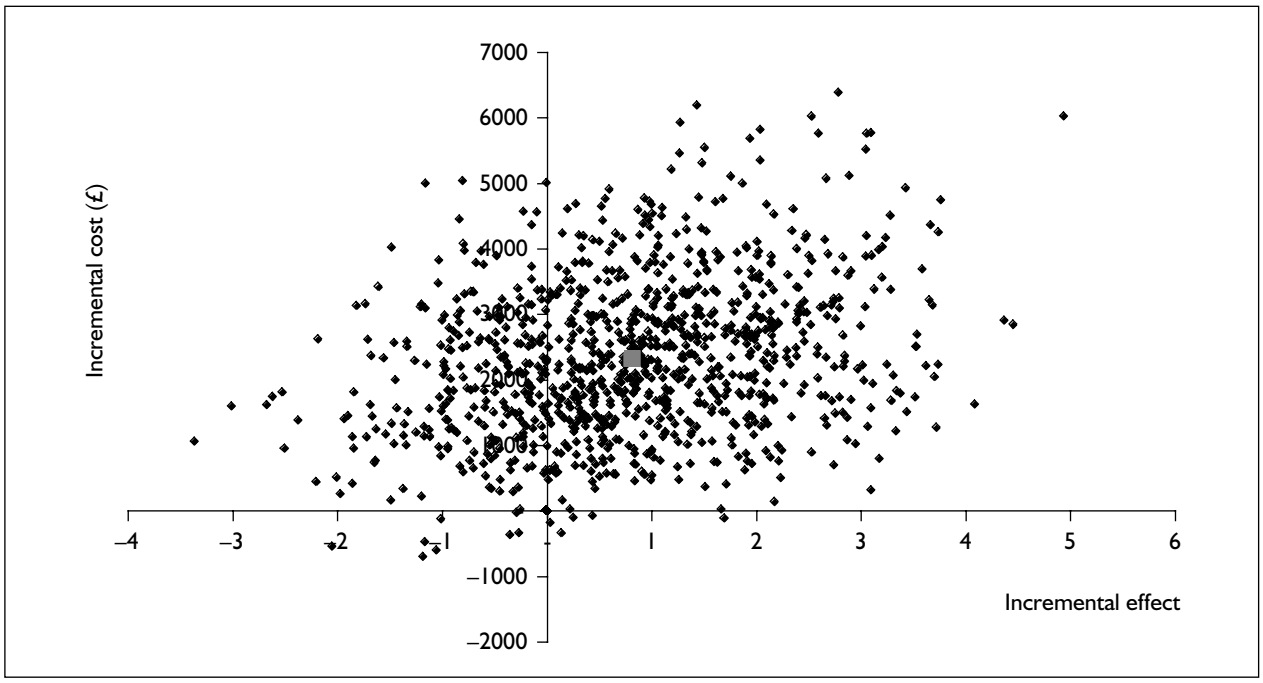

FIGURE 8 *Scatterplot showing the bootstrapped mean differences in costs and effects using the HoNOSCA*

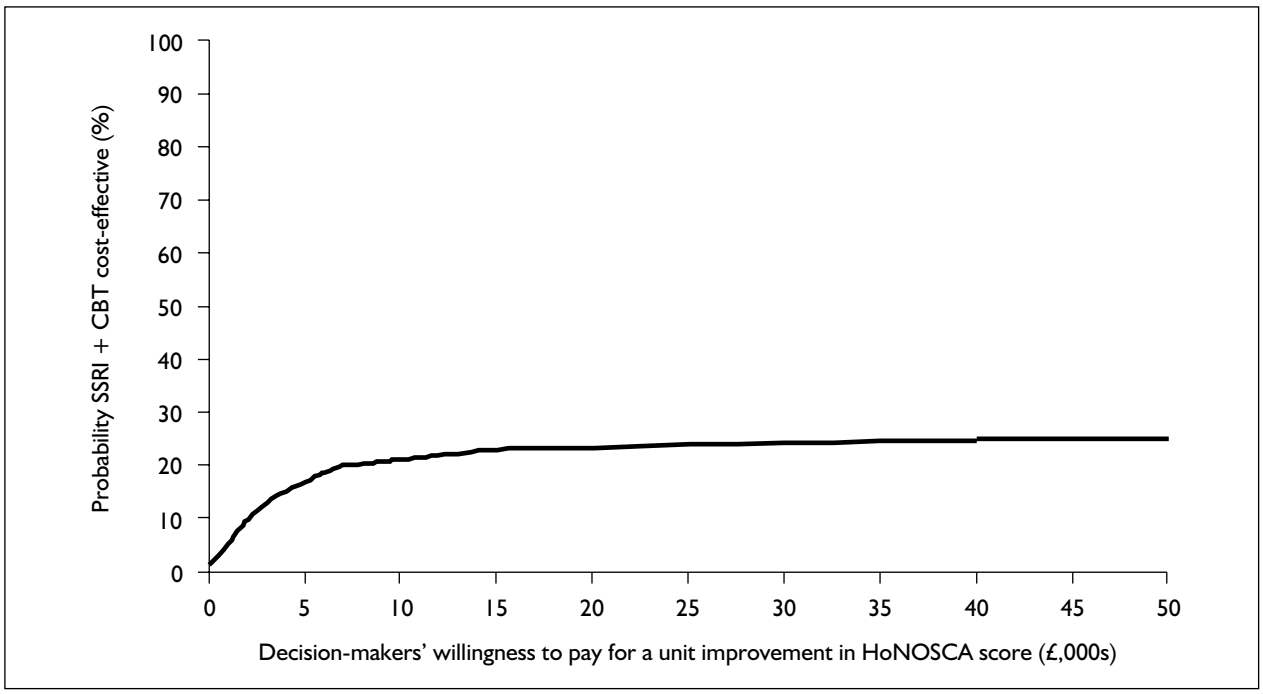

FIGURE 9 *CEAC for HoNOSCA showing the probability that SSRI + CBT is more cost-effective than SSRIs only*

associated with poorer outcomes for a large proportion of replications (points to the right of the *y*-axis). *Figure 9* illustrates the associated uncertainty and demonstrates that there is at best a 26% chance of SSRI + CBT being more cost-effective than SSRI over the full range of values of the ceiling ratio.

The relationship was similar for QALYs, with the SSRI + CBT group being more expensive than the

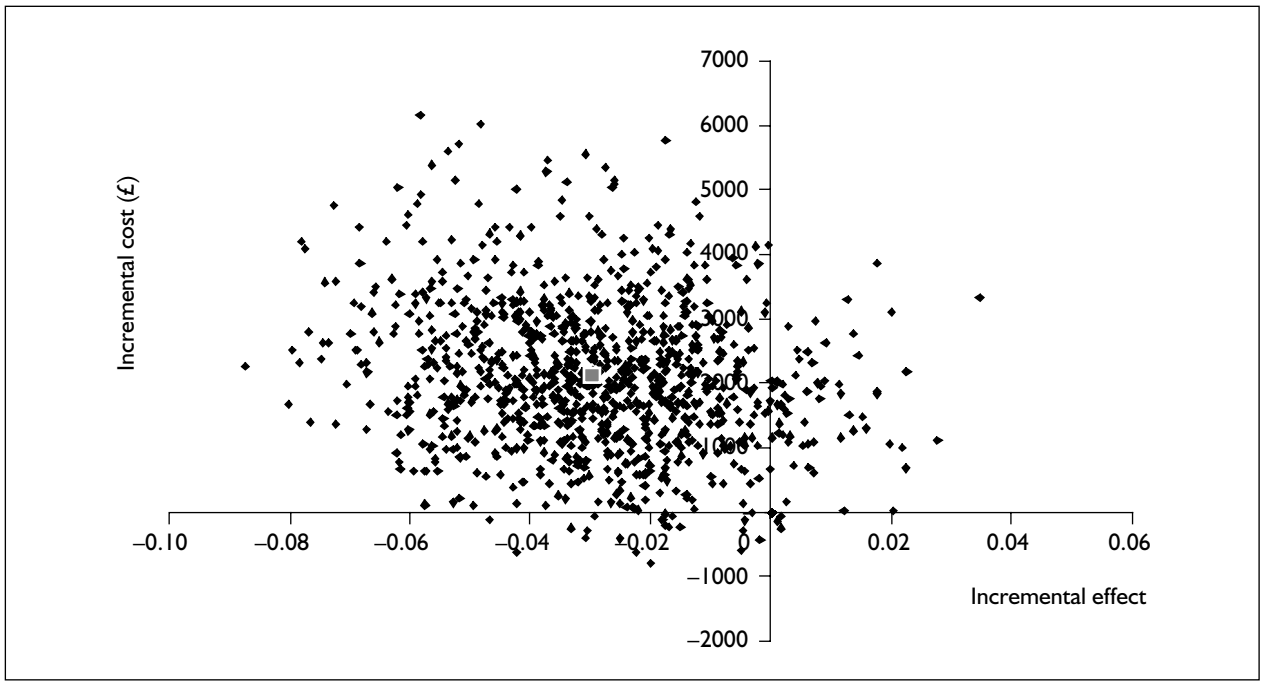

FIGURE 10 *Scatterplot showing the bootstrapped mean differences in costs and effects using QALYs*

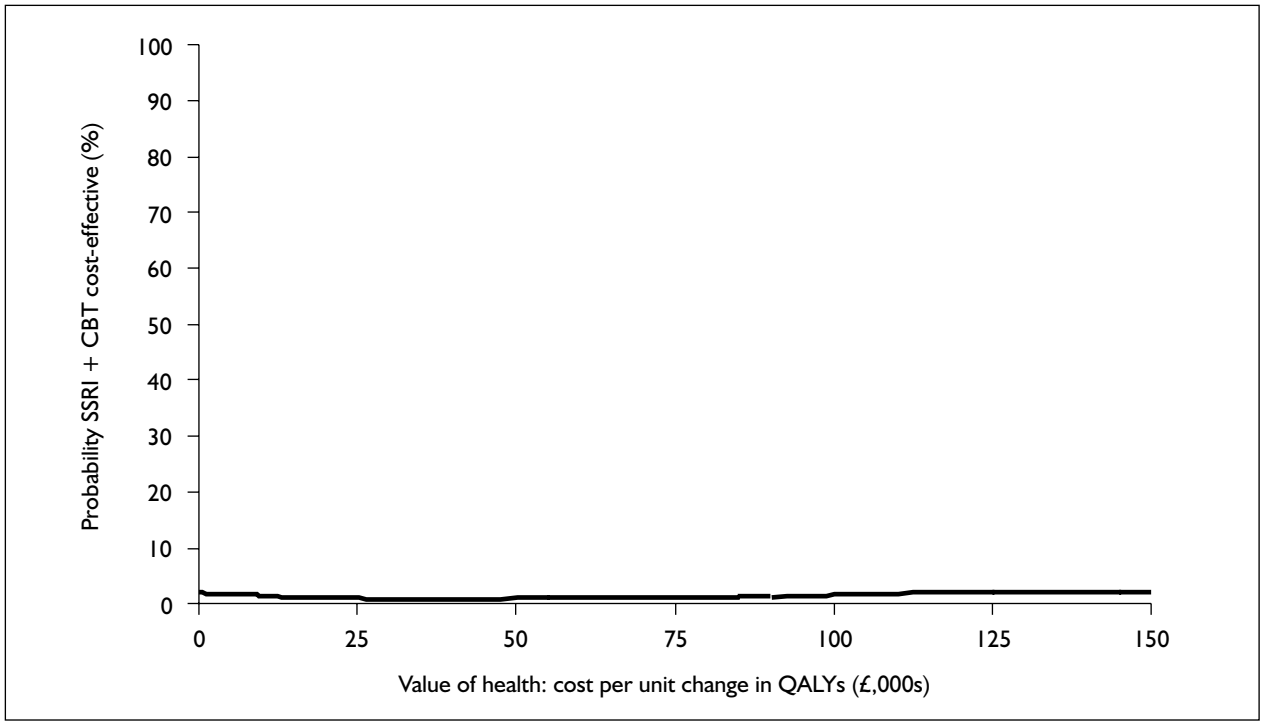

FIGURE 11 *CEAC for QALYs showing the probability that SSRI + CBT is more cost-effective than SSRIs only*

SSRI only group and less effective (bootstrapped incremental mean costs £2115; bootstrapped incremental mean effects –0.0297), with an ICER of –£71,212, where higher scores indicate better outcomes. The scatterplot for QALYs is shown in *Figure 10*. The CEAC showing the probability of SSRI + CBT being more cost-effective than SSRI only did not rise above 2% (*Figure 11*).

Primary carer use of resources and costs

Use of resources by the young person's primary carer and associated costs are reported in *Tables 25* and *26*. Very few differences are evident. Overall the primary carers of the SSRI + CBT group cost slightly more than those of the SSRI only group, but this difference was not statistically significant. There were also no differences over time (*Table 27*).

TABLE 25 *Use of health and community resources by primary carer during the 28-week follow-up period: mean per patient*

Service	Use of resources; mean (SD)		Proportion using service (%)
	SSRI + CBT (*n* = 91)	SSRI only (*n* = 90)	
Hospital services			
Inpatient days	2.5 (16.1)	1.2 (6.2)	12
Outpatient contacts	1.5 (3.3)	1.8 (3.3)	44
Day patient contacts	0.1 (0.3)	0.2 (0.6)	9
Accident and emergency	0.2 (0.7)	0.2 (0.5)	14
Community services			
GP	4.6 (9.5)	4.2 (6.1)	77
Practice nurse	0.5 (1.1)	0.6 (1.5)	29
Medication	30%	43%	36
Social worker	0.3 (1.4)	0.7 (3.0)	12
Counsellor	0.1 (0.6)	0.8 (3.6)	8
Community psychiatric nurse	0.4 (2.3)	0.2 (1.4)	3
Community psychiatrist	0.0 (0.3)	0.0 (0.2)	2
District nurse	0.0 (0.0)	0.1 (0.6)	1
Physiotherapist	0.0 (0.0)	0.1 (0.4)	1
Health visitor	0.0 (0.0)	0.0 (0.4)	0
Private healthcare	0.7 (4.5)	0.2 (1.2)	4

TABLE 26 *Total health and community service costs per primary carer over the 28-week follow-up period (£)*

	Mean (SD)		Mean difference (95% CI)	*p*-Value
	SSRI + CBT (*n* = 91)	SSRI only (*n* = 90)		
Health services	865 (3794)	625 (1421)	240 (–602 to 1082)	
Social services	9 (46)	22 (96)	–13 (–35 to 9)	
Private sector services	21 (143)	5 (28)	16 (–14 to 47)	
Travel	31 (39)	17 (17)	13 (4 to 22)	
Lost productivity	236 (1011)	296 (1714)	–60 (–472 to 352)	
Total costs	1162 (3878)	965 (2178)	196 (–728 to 1120)	0.590

TABLE 27 *Change in primary carers' costs over time: mean per week (£)*

	Mean (SD)		Mean difference (95% CI)	*p*-Value
	SSRI + CBT (*n* = 91)	SSRI only (*n* = 90)		
Baseline	14 (32)	14 (22)	–0 (–8 to 8)	0.844
12-Week follow-up[a]	39 (148)	26 (50)	13 (–20 to 45)	0.348
28-Week follow-up[a]	42 (131)	36 (112)	6 (–30 to 42)	0.644

[a] Excludes travel and productivity costs for comparison, as these were not collected at baseline.

TABLE 28 *Univariate associations with cost over 28 weeks*

Variable	*N*	Mean cost (£)	*p*-Value
Age (years)			
⩽14	84	6350	0.000
>14	73	4030	
Sex			
Male	44	6377	0.178
Female	113	4841	
Ethnicity			
White	153	5209	0.448
Non-white	4	7679	
Centre			
Manchester	106	5487	0.554
Cambridge	51	4822	
Depression severity			
Moderate	70	5104	0.770
Severe	87	5406	
Behavioural disorder			
Yes	45	5269	0.994
No	112	5277	
Suicidal ideation			
Not present/sub-threshold	93	5638	0.389
Threshold	64	4739	
Mother's wellbeing (GHQ)			
⩽31	84	5655	0.883
>31	73	4830	

TABLE 29 *Multivariate associations with cost over 28 weeks*

Variable	Coefficient[a] (95% CI)	*p*-Value
Age at initial interview[b]	–1450 (–2235 to –665)	0.000

[a] Adjusted $R^2 = 0.073$.
[b] The coefficient indicates the decrease in cost over 28 weeks per unit increase in the variable.

Cost–function analysis

Variables examined in the cost–function analysis are reported in *Table 28*. Univariate analysis revealed that higher total costs were significantly associated with younger age. Age remained the only variable significantly and independently related to cost in multiple regression analysis (*Table 29*). The results demonstrate that for each year of reduction in age, total costs increased by £1450. The regression model was able to account for less than 10% of the variation in total costs (adjusted $R^2 = 0.073$), suggesting substantial unexplained variation in this group of young people.

Summary of economic analysis

Although improvements on the EQ-5D were evident in the group as a whole, these young people were still reporting scores lower than the UK population norm of 86.49 for young people under 25 years of age.[52]

The SSRI + CBT treatment group was found to be more expensive over the 28-week follow-up than the SSRI only group. This was not a significant finding at the 5% level, but the result came close to statistical significance. As would be expected, the SSRI + CBT group was significantly more expensive than the SSRI only group in terms of the intervention sessions received. However, differences in cost were in fact driven by much higher secondary healthcare costs in the SSRI + CBT group, primarily inpatient costs resulting from two young people in that group who spent the majority of the follow-up period in hospital. Exploration of the impact of these individuals in sensitivity analysis did not suggest that their

exclusion would significantly alter the results. The addition of the cost of DNAs and the cost of supervisors' time increased the cost difference to the extent that the SSRI + CBT group became significantly more expensive in both analyses.

Cost-effectiveness analysis further emphasises the lack of evidence in favour of SSRI + CBT. Irrespective of the measure of outcome chosen, there was no evidence to support the hypothesis that SSRI + CBT is a more cost-effective strategy than SSRI only medication for adolescents with major depression in receipt of routine care. CEACs suggest that there is at best a 26% probability that SSRI + CBT is more cost-effective than SSRI only in terms of the HoNOSCA and only a 2% probability in terms of QALYs gained. Even when the two high-cost SSRI + CBT individuals were excluded in an attempt to bias the results in favour of SSRI + CBT, the probability of being cost-effective remained less than 50%.

Only age at trial entry was found to be significantly related to costs in univariate and multivariate analyses. This replicates earlier findings that costs decrease with age in child and adolescent populations.[74,77]

Analysis of patients excluded due to missing economic data found only a significant centre difference, with a much higher proportion of missing data in Manchester than Cambridge. However, follow-up rates were relatively high (90%) and there is no evidence to suggest that the comparison of the two treatment groups was biased as a result of missing data.

Summary of results for the ADAPT trial

SSRI + CBT for adolescents with persistent moderate to severe major depression did not result in significant benefits compared with SSRI only over 28 weeks. Self-rated health status showed consistent improvements over time in both groups, but there were no between-group differences.

There is no economic justification for including CBT with fluoxetine as the treatment of choice in those non-responsive to a brief psychosocial approach. Both treatments were equally effective in the short term and CBT was associated with additional costs.

Treatment response may show a variable undulating rather than a linear response in some cases. Around 21% may be persistently moderately to severely depressed despite receiving adequate treatment. Amongst these, 9% show no change and 5% minimal and 7% moderate to severe deterioration.

Chapter 9
Conclusions

- A brief (2-week) psychoeducational intervention (BII) may be effective in a proportion of clinic referrals with moderate to severe major depression.
- SSRI, specifically fluoxetine, together with ACC, is the preferred treatment of choice in adolescents referred to CAMHS services and diagnosed with moderate to severe major depression who are not responsive to BII.
- ACC + fluoxetine treatment with or without CBT is associated with clinical improvement (symptom reduction, suicidality and improved psychosocial function) over the duration of the trial.
- There is no economic value in adding CBT to ACC + fluoxetine as the increase in costs is not offset by any health gains or reductions in use of other hospital, community and education services.
- Clinical response to medication may take at least 12 weeks in a proportion of patients.
- The pattern of treatment response may undulate over the full trial period. Subjective reporting of no change or even feeling less well at one assessment may not be indicative of treatment resistance over the full trial period.
- After 7 months of active treatment, one in 10 of depressed adolescents appear likely to be reporting low or no response to fluoxetine with or without CBT. These are likely to be treatment-resistant cases to fluoxetine with or without CBT.
- Fluoxetine + ACC is not associated with an increase in suicidal thoughts or actions, self-harm or other adverse events.
- There is no evidence of a protective effect of CBT on suicidality in adolescents being treated with fluoxetine plus clinical care.
- In the presence of ACC, the probability of a fluoxetine-induced disinhibition syndrome comprising markedly raised irritability and/or hypomania together with increased risk of violence to self or others appears to be negligible.
- The study cannot conclude that fluoxetine only would be effective in unipolar depression as there was no fluoxetine only arm without ACC in this study. Delivery of fluoxetine only without routine specialist ACC is unlikely to be considered best practice in specialist CAMHS in the UK.
- In policy terms, the findings may be best applied to patients with unipolar depressions characterised by high (>6) levels of depressive symptoms, increased risk for suicidality, marked psychosocial impairment (CGAS < 50) and at least one co-morbid disorder likely to contain levels of worry, phobic or compulsive behaviours.

Chapter 10
Discussion

There was no support for the hypothesis that, in the presence of routine specialist clinical care, SSRI + CBT would have a significantly better outcome than SSRI only treatment. These findings are consistent with one recent trial that tested the effects of combined treatment against SSRIs alone,[77] but differed from the Treatment for Adolescents with Depression Study (TADS), which showed combined treatment to be more effective than fluoxetine alone on some but not all of the outcome measures.[78] This was only true, however, for cases of moderate, and not severe, depression in the TADS study. The failure to establish greater therapeutic effect from combined treatment is also consistent with recent studies noting the lack of effectiveness for CBT alone (i.e. without the equivalent of ACC as practised in CAMHS NHS settings) as a first-line treatment in facilitating clinical remission for moderate to severe major depression.[77,78] A recent reanalysis of TADS has also found that combined treatment does not offer any advantages over fluoxetine in the most impaired cases, consistent with our findings.[79] We had planned to determine if CBT may accelerate time to remission and thereby improve cost-effectiveness of inclusion as a treatment even if proportion recovered at a given end-point of 12 weeks was the same. Unfortunately, we could not test for a time to remission effect because the recording of the offset of symptoms required to calculate precise timing of remission was not reliable.

The absence of a control group receiving no treatment was considered unethical. A contrast group receiving active routine clinical care only could have provided a test of the added clinical effectiveness of an SSRI. A CBT only arm would have provided an active test of the efficacy of CBT compared with SSRI only with ACC. Hence we cannot determine if improvement is due directly to treatment given as spontaneous remission may have accounted for a proportion of those recovered by 12 and 28 weeks. Similarly, we cannot determine the precise therapeutic effectiveness of fluoxetine without some form of control or comparison group. The trial did not set out to test efficacy or effectiveness for the active treatments, but interpretation of the results needs to be understood within the limitations of the design used.

Considerable concerns have been raised regarding the use of SSRIs in adolescents because of the observation that the risks might outweigh the benefits. Only fluoxetine has been shown to be both effective and safe when published and unpublished data have been pooled.[80] The current findings support the safety of fluoxetine as a treatment for depressed adolescents. Whether this is because of the clinical context within which medication is delivered (i.e. relatively regular ACC throughout the trial) deserves further study.

The ADAPT methodology has dealt with a large number of the criticisms levelled at previous RCTs of medication in young people[81] as follows: there is no funding from commercial sources; the sample size is adequate; retention of participants is very high (>90%); ITT analysis has been used; a range of outcome measures have been examined. A limitation in design is the absence of a CBT only arm preventing a full comparison of the three treatment options available from the candidate therapies chosen.

A further key strength of ADAPT is that the sample studied closely reflects a typical CAMHS population, with a significant degree of severity, co-morbidity, suicidality and also psychosis. The participants were not recruited through advertisements, and therefore the results are particularly relevant to the type of patients seen in the NHS. In addition, this study is unique as it is a true effectiveness study of NHS treatment, not an efficacy trial of gold-standard treatment with a highly selected patient group. Therefore, a variety of CBT therapists with different levels of experience were used, as would occur in real-life practice. Although the quality of therapy varied, the majority of rated CBT sessions were of adequate quality and this did not affect the outcome. Attendance rates were not as high as in TADS, but the TADS sample was significantly less impaired and suicidal, recruited through advertisements, and was based in the USA, where there is high motivation to participate in a treatment trial which provides free treatment.

Hence the two samples are not directly comparable. In addition, attendance rates were not dissimilar to those in another more pragmatic trial.[77] The current findings demonstrate that CBT is not easy to deliver in CAMHS. Although a high-dose (19 sessions) CBT plan was implemented in the SSRI + CBT arm, few adolescents achieved more than 10 sessions in total. In addition to showing an added value to outcome, the attendance data suggest that this treatment appears to be difficult to deliver and perhaps to receive in this age range in routine CAMHS settings.

A potential limitation of ADAPT is that psychiatrists provided both CBT and the treatment in the SSRI only arm, so cross-contamination may be a possibility. However, this is unlikely as the SSRI only sessions were fewer and briefer, comparatively unstructured, not goal directed, no homework was set, the CBT model was not discussed and there was no focus on cognitions. There was some overlap with general principles of depression treatment, mainly discussion of increasing activities, but this was part of the routine clinical care of depression. Therefore, if cross-contamination did occur, it would have been minimal and not comparable to a formal course of CBT. We are, however, examining this issue further in an analysis of the SSRI only taped sessions. Despite any such potential limitations of this study, the results are supported by other trials of combined treatment with differing methodologies.[77,78,82]

The evidence from the pretrial BII is that a number of depressions presenting to clinical services may respond to relatively straightforward psychological interventions. This suggests that further systematic exploration of psychological treatment components embedded within our BII strategy in outpatient settings is an important next step. BII was not compared with a non-intervention control group, so it is not possible to know how much of this improvement could be attributed to spontaneous remission. Furthermore, the current results clearly indicate that if such psychological interventions are ineffective in moderate to severe cases in symptom reduction and improving personal function within 2–4 weeks, the addition of fluoxetine results in a pragmatically effective treatment.

A key additional shortcoming in this study is the follow-up period. Ending evaluations at 28 weeks prevents any investigation of longer term effects of CBT or an investigation of relapse prevention. Psychological treatments may work as a first-line treatment in severe depressions but only over a much longer period. Hence combined treatment may not show effects until much later. In addition, recurrence risk may be reduced in those with a combined treatment, as has been shown in adult studies.[83] Neither of these effects can be evaluated except through much longer term follow-up.

Future studies should also consider broader outcome variables than symptom reduction and general psychosocial functioning. For example, from the health services perspective further consideration should be given to measuring the efficiency and effectiveness of the care pathway and delivery processes required to ensure that the best treatments reach the correct patients as soon as possible. There are five key areas to consider as a result in part of the ADAPT findings.

First, investigating whether or not there are marked differences between CAMHS organisations in resource allocation, ease of delivery and cost-effectiveness of evidence-based treatments for depressed adolescents should be a clinical research priority. A key feature of the ADAPT trial was that all participants had an assessment and clinical care provided by child psychiatrists, and it is not clear how the results would generalise to other CAMHS professionals with varying levels of training and experience.

Second, there may be differential sensitivity to treatment depending on the evolving nature of the depression. Hence the relative efficacy of BII procedures even for moderate to severe depressions deserves further investigation. For example, if BII can be clearly characterised and efficiently delivered there may be a treatment approach that has greater effects in emergent depressive disorders in primary care settings than considered hitherto. This remains to be systematically evaluated.

Third, we remain ignorant of whether adjunctive treatments may be important in preventing relapse even if they show fewer efficacies in treating first episodes. The psychotherapies may have a key role in relapse prevention and reducing economic costs of subsequent healthcare in this age range, but this remains to be determined. Which techniques are required to effect relapse prevention in young people require further study. Might this be achieved by techniques more akin to BII together with attending to the holistic needs of the developing youngster (including mental hygiene and physical well-being)? Or will more specific psychological treatments such as CBT be required?

Fourth, the finding that around 20% of cases may be non-responders is a serious clinical issue for specialist CAMHS services. Indeed, around 12% of cases were actually worse after entering treatment. A significant proportion of these are likely to persist and become a significant clinical and economic burden to the public sector over the subsequent two decades.[11,18] It is not clear if this is a result of non-compliance with treatments or true treatment resistance. Given that depression is a disorder with a high risk for recurrence, persistence and/or relapse into adult life, and there have been no long-term studies of adolescent treatment non-responders, there is a clear healthcare and economic imperative to investigate this putative treatment resistant group further.

Fifth, the findings of individual differences in treatment response highlight the need to identify at assessment factors that will aid in predicting outcome following treatment. Prior research suggests that persistence and poor psychosocial function 18 months after presentation are likely to be due to a combination of factors, some of which are social (e.g. persistent peer group isolation), clinical (e.g. the presence of obsessive–compulsive disorder), pathophysiological (e.g. cortisol hypersecretion) and psychological (e.g. high levels of mood-related ruminative style).[28,29,84,85,86]

The findings highlight the poor precision of current clinical measurement tools for determining sensitivity and response to treatment. This is a serious defect for both the clinical scientific study of depression and the planning of services. For the former, although we have clues regarding the pathophysiology of the depressions, we have yet to introduce deliverable and useful tests to the clinical workplace to help predict treatment response. For the latter, practitioners have no tools to help them determine the best treatment package for their patients and continue to have to rely on 'best estimates' derived from routine clinical assessment.

The overall absence of adverse events and the decline in suicidal risk in the trial cohort are extremely encouraging for the reduction in morbidity in this population over the adolescent years. The findings are a very positive inducement to primary care trusts to fund treatment services for currently depressed youth.[87] These findings highlight the importance of rapid access and active treatment for severe depression, given that depression during the adolescent years is a significant indicator of recurrence risk in adult life.[11] There is therefore an important public health need to intervene in this serious mental illness in young people as actively and rapidly as possible.[88]

Clinical recommendations

1. As a best practice point, adolescents with a diagnosis of unipolar major depression should receive a brief psychosocial intervention (BII) consisting of (a) education about their condition; (b) advice on general well-being (mental and physical); (c) parent support; and (d) help in problem solving adverse consequences arising from recent negative life events. This could be delivered relatively easily in specialist CAMHS settings and may be clinically effective in some cases.
2. In those unresponsive to BII within 2–4 weekly sessions, fluoxetine should be added together with continuing specialist psychosocial management.
3. Monitoring of progress should take into account the potential for an undulating course of improvement following the start of treatment. Within the first 6 weeks some patients may complain of feeling somewhat worse before improvement occurs.
4. As the most rapid improvement is normally seen in the early phases of treatment, non-improvement by 12 weeks should result in a full clinical review.

Recommendations for future research

1. **Evaluate the efficacy of specific psychological treatments against brief psychological intervention.** The current findings provide anecdotal findings for the putative effectiveness of BII for some cases of depression. BII can most likely be delivered by all routine CAMHS services. It is not clear if BII would be as safe and effective as CBT, family or interpersonal psychotherapy (IPT) for adolescents with moderate depressions.
2. **Determine the characteristics of patients with severe depression that are non-responsive to fluoxetine.** It is likely that non-responders will be heavy healthcare users into adult life. Delineating their characteristics and their pattern of healthcare use, including compliance with treatment offered as adolescents, would be a key study.
3. **A study into relapse prevention in severe depressions.** Preventing relapse will reduce the

risks associated with multiple depressive episodes. Candidate models include assertive outreach, dealing with non-health barriers to rehabilitation (education, skills development and work entry); CBT or IPT in healthcare settings: family therapies to reduce negative environments in the home; befriending techniques to re-engage the adolescent peer group often lost during a depressive episode. Relapse prevention may improve outcome into adult life and diminish healthcare costs in the medium term. A longer term study with follow-up for 2 years post-remission is required to address these questions.

4. **Improve the tools for determining treatment responders and non-responders.** A weakness in all trials to date, including ADAPT, is the precision of measurement to assess both the nature of the disorder and treatment response. New tools are urgently required. These should go beyond surface aspects of the phenotype. Such research must also determine the most efficient delivery mode to the clinic of any new and valid test procedure and its cost benefits to the service.
5. **Improve the tools for determining treatment responders and non-responders.** A weakness in all trials to date, including ADAPT, is the precision of measurement to assess both the nature of the disorder and treatment response. New tools are urgently required. These should go beyond surface aspects of the phenotype. They could include neuropsychological measures relating to performance, mood-related measures of cognitive style that predict persistence of an episode, physiological measures such as cortisol hypersecretion during an episode that predict a chronic course and genetic variations such as the 's' allele of the serotonin promoter gene (5-HTTPLR) which influence risk for depressive onsets and perhaps response to SSRIs. Such research must also determine the most efficient delivery mode to the clinic of any new and valid test procedure and its cost benefits to the service.

ADAPT and the National Institute for Health and Clinical Excellence (NICE) guidelines on depression in young people

The NICE guidelines recommend that 'Antidepressant medication should not be offered to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy'. This study has demonstrated that adding CBT to fluoxetine confers no extra benefit to, and may be more expensive than, providing good-quality clinical care alongside fluoxetine. This limited resource of CBT may be better deployed for other indications than using it routinely for all depressed adolescents taking fluoxetine. The findings cannot comment on who is in the best position to prescribe.

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Contribution of authors

Ian Goodyer (Professor of Child and Adolescent Psychiatry) designed the study, obtained the research funding and wrote papers arising from the study. Bernadka Dubicka (Consultant in Adolescent Psychiatry) and Paul Wilkinson (Clinical Lecturer in Child and Adolescent Psychiatry) undertook clinical assessments, medical management and CBT and wrote papers arising from the study. Raphael Kelvin (Consultant Child and Adolescent Psychiatrist) provided clinical supervision, case management and wrote papers from the study. Chris Roberts (Senior Lecturer in Medical Statistics) undertook statistical analysis of data and wrote papers. Sarah Byford (Senior Lecturer in Health Economics) did the health economics design, related statistical analysis and with Barbara Barrett (Research Worker in Health Economics) wrote papers from the study. Siobhan Breen (Trainee, Clinical Psychology Unit), Claire Ford (Health Psychologist), Alison Leech (Consultant Child and Adolescent Psychiatrist) and Justine Rothwell (Research Associate) conducted research assessments of the patients. Lydia White (Trial Manager) co-ordinated trial data, maintained databases and managed the overall administration of the trial. Richard Harrington (former Professor of Child Psychiatry) designed the study and obtained the research funding.

Papers published in other peer-reviewed journals relating to this research project

Byford S, Barrett B, Roberts C, Wilkinson P, Dubicka B, Kelvin RG, *et al*. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. *Br J Psychiatry* 2007;**191**: 521–7.

Dubicka B, Wilkinson P. Evidence based treatment of adolescent major depression. *Evid Based Ment Health* 2007;**10**:100–2.

Goodyer I, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ* 2007;**335**:142.

Harrington RC, Cartwright-Hatton S, Stein A. Annotation: randomised trials. *J Child Psychol Psychiatry* 2002;**43**:695–704.

Harrington R, Dubicka B. Adolescent depression: an evidence-based approach to intervention. *Curr Opin Psychiatry* 2002;**15**:369–75.

Wilkinson PO, Goodyer IM. The effects of cognitive-behavioural therapy on mood-related ruminative response style in depressed adolescents. *Child Adolesc Psychiatry Ment Health* 2008;**2**:3.

References

1. Angold A, Costello EJ. The epidemiology of depression in children and adolescents. In Goodyer I, editor. *The depressed child and adolescent*. 2001, Cambridge: Cambridge University Press. pp. 143–78.
2. Ford T, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:1203–11.
3. Green H, McGinnity A, Meltzer H, Ford T, Goodman R. Mental health of children and young people in Great Britain – 2004. *National Statistics*. London: HMSO; 2005.
4. Collishaw S, Maughan B, Goodman R, Pickles A. Time trends in adolescent mental health. *J Child Psychol Psychiatry* 2004;**45**:1350–62.
5. Fombonne E. Increased rates of psychosocial disorders in youth. *Eur Arch Psychiatry Clin Neurosci* 1998;**248**:14–21.
6. Fombonne E. Increased rates of depression: update of epidemiological findings and analytical problems. *Acta Psychiatr Scand* 1994;**90**:145–56.
7. Fombonne E. Depressive disorders: time trends and their possible explanatory mechanisms. In Rutter M, Smith D, editors. *Psychosocial disorders in young people*. Chichester: Wiley, 1995. pp. 544–615.
8. Harrington RC, Dubicka B. Natural history of mood disorders in children and adolescents. In Goodyer I, editor. *The depressed child and adolescent*. Cambridge: Cambridge University Press; 2001. pp. 311–43.
9. Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression. 1. Psychiatric outcomes in adulthood. *Br J Psychiatry* 2001; **179**:210–17.
10. Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression. 2. Suicidality, criminality and social dysfunction in adulthood. *Br J Psychiatry* 2001;**179**:218–23.
11. Dunn V, Goodyer IM. Cambridge adolescent depression follow-up study: psychiatric outcomes. *Br J Psychiatry* 2006;**188**:216–22.
12. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 1999; **156**:837–41.
13. Goodyer IM, Herbert J, Tamplin A, Altham PM. First-episode major depression in adolescents. Affective, cognitive and endocrine characteristics of risk status and predictors of onset. *Br J Psychiatry* 2000;**176**:142–9.
14. Lewinsohn PM, Allen NB, Seeley JR, Gotlib IH. First onset versus recurrence of depression: differential processes of psychosocial risk. *J Abnorm Psychol* 1999;**108**:483–9.
15. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 1992;**149**:999–1010.
16. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry* 2000; **157**:1243–51.
17. Boys A, Farrell M, Taylor C, Marsden J, Goodman R, Brugha T, *et al*. Psychiatric morbidity and substance use in young people aged 13–15 years: results from the Child and Adolescent Survey of Mental Health. *Br J Psychiatry* 2003; **182**:509–17.
18. McCrone P, Knapp M, Fombonne E. The Maudsley long-term follow-up of child and adolescent depression: predicting costs in adulthood. *Eur J Child Adolesc Psychiatry* 2005;**14**:407–13.
19. Kovacs M. The Emanuel Miller Memorial Lecture 1994. Depressive disorders in childhood: an impressionistic landscape. *J Child Psychol Psychiatry* 1997;**38**:287–98.
20. Harrington R, Campbell F, Shoebridge P. Meta-analysis of CBT for depression in adolescents. *J Am Acad Child Adolesc Psychiatry* 1998;**37**:1005–7.
21. Reinecke MA, Ryan NE, DuBois DL. Cognitive–behavioral therapy of depression and depressive symptoms during adolescence: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1998;**37**:26–34.
22. Jayson D, Wood A, Kroll L, Fraser J, Harrington R. Which depressed patients respond to cognitive-behavioral treatment? *J Am Acad Child Adolesc Psychiatry* 1998;**37**:35–9.
23. Taskforce American Academy of Child and Adolescent Psychiatry. Practice paramaters for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 1998;**37**(Suppl 10):63s–83s.
24. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, *et al*. A double-blind,

randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 1997;**54**:1031–7.

25. Kutcher S. *Child and adolescent psychopharmacology*. Philadelphia, PA: Saunders; 1997.
26. Leonard HL, March J, Rickler KC, Allen AJ. Pharmacology of the elective serotoninreuptake inhibitors in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:725–36.
27. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. *Arch Gen Psychiatry* 2005;**62**:66–72.
28. Goodyer IM, Park RJ, Herbert J. Psychosocial and endocrine features of chronic first-episode major depression in 8–16 year olds. *Biol Psychiatry* 2001; **50**:351–7.
29. Goodyer IM, Herbert J, Tamplin A. Psychoendocrine antecedents of persistent first-episode major depression in adolescents: a community-based longitudinal enquiry. *Psychol Med* 2003;**33**:601–10.
30. Goodyer IM, Herbert J, Secher SM, Pearson JL. Short-term outcome of major depression: I. Comorbidity and severity at presentation as predictors of persistent disorder. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:179–87.
31. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:980–8.
32. Costello EJ, Angold A. Scales to assess child and adolescent depression: checklists, screens and nets. *J Am Acad Child Adolescent Psychiatry* 1988;**27**:726–37.
33. Costello EJ, Angold A, Burns BJ, Stangl DK, Tweed DL, Erkanli A, *et al*. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. *Archi Gen Psychiatry* 1996;**53**:1129–36.
34. Wood A, Kroll L, Moore A, Harrington RC. Properties of the mood and feelings questionnaire: a research note. *Journal Child Psychol Psychiatry* 1995; **36**:327–34.
35. Kent L, Vostanis P. Detection of major and minor depression in children and adolescents: evaluation of the Mood and Feelings Questionnaire. *J Child Psychol Psychiatry* 1997;**38**:565–73.
36. Gowers SG, Harrington RC, Whitton A, Lelliott P, Beevor A, Wing J, *et al*. Brief scale for measuring the outcomes of emotional and behavioural disorders in children. Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA). *Br J Psychiatry* 1999;**174**:413–16.
37. Garralda ME, Yates P, Higginson I. Child and adolescent mental health service use. HoNOSCA as an outcome measure. *Br J Psychiatry* 2000;**177**:52–8.
38. Bilenberg N. Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) – results of a Danish field trial. *Eur Child Adolesc Psychiatry* 2003;**12**:298–302.
39. Brann P, Coleman G, Luk E. Routine outcome measurement in a child and adolescent mental health service: an evaluation of HoNOSCA. The Health of the Nation Outcome Scales for Children and Adolescents. *Aust NZ J Psychiatry* 2001; **35**:370–6.
40. Guy W. *ECDEU assessment manual for psychopharmacology*. Washington, DC: US Government Printing Office; 1976.
41. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, *et al*. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry* 1983; **40**:1228–31.
42. Schorre BE, Vandvik IH. Global assessment of psychosocial functioning in child and adolescent psychiatry. A review of three unidimensional scales (CGAS, GAF, GAPD). *Eur Child Adolesc Psychiatry* 2004;**13**:273–86.
43. Dyrborg J, Larsen FW, Nielsen S, Byman J, Nielsen BB, Gautre-Delay F. The Children's Global Assessment Scale (CGAS) and Global Assessment of Psychosocial Disability (GAPD) in clinical practice – substance and reliability as judged by intraclass correlations. *Eur Child Adolesc Psychiatry* 2000; **9**:195–201.
44. Poznanski EO, Cook SC, Carroll BJ. A depression rating scale for children. *Pediatrics* 1979;**64**:442–50.
45. Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the children's depression rating scale. *J Am Acad Child Psychiatry* 1984;**23**:191–7.
46. Zalsman G, Misgav S, Sommerfeld E, Kohn Y, Brunstein-Klomek A, Diller R, *et al*. Children's Depression Inventory (CDI) and the Children's Depression Rating Scale – Revised (CDRS-R): reliability of the Hebrew version. *Int J Adolesc Med Health* 2005;**17**:255–7.
47. Klein RG. *Lifetime Schedule for Affective Disorders and Schizophrenia for Adolescents (12–19 years). Kiddie-SADS-Lifetime (K-SADS-L)*. Pittsburgh, PA: University of Pittsburgh; 1993.
48. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med* 1979; **9**:139–45.
49. Bamber D, Tamplin A, Park RJL. Development of a short Leyton obsessional inventory for children and adolescents. *J Am Acad Child Adolesc Psychiatry* 2002; **41**:1246–52.

50. Tamplin A, Goodyer IM. Family functioning in adolescents at high and low risk for major depressive disorder. *Eur Child Adolesc Psychiatry* 2001;**10**:170–9.

51. Tamplin A, Goodyer IM, Herbert J. Family functioning and parent general health in families of adolescents with major depressive disorder. *J Affect Disord* 1998;**48**:1–13.

52. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. Centre for Health Economics Discussion Paper 172. York: University of York; 1999.

53. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37**:53–72.

54. Brooks R, Kerridge R, Hillman K, Bauman A, Daffurn K. Quality of life outcomes after intensive care. Comparison with a community group. *Intensive Care Med* 1997;**23**:581–6.

55. Williams A. *The role of the EuroQol instrument in QALY calculations*. Centre for Health Economics Discussion Paper 130. York: University of York; 1995.

56. Byford S, Harrington R, Torgerson D, Kerfoot M, Dyer E, Harrington V, *et al*. Cost-effectiveness analysis of a home-based social work intervention for children and adolescents who have deliberately poisoned themselves. Results of a randomised controlled trial. *Br J Psychiatry* 1999;**174**:56–62.

57. Netten A, Knight J, Dennett J, Cooley R, Slight A. *Ready reckoner for staff costs in the NHS*. Canterbury: Personal Social Services Research Unit, University of Kent; 1998.

58. British Medical Association and Royal Pharmaceutical Society. *British National Formulary 48*. London: BMJ Books/Pharmaceutical Press; 2004.

59. Department of Health. *NHS reference costs*. London: Department of Health; 2004.

60. Curtis L, Netten A. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit, University of Kent; 2004.

61. Berridge D, Beecham J, Brodie I, Knapp M. *Costs and consequences of services for troubled adolescents: an exploratory, analytic study*. Report to the Department of Health. London: Department of Health; 2002.

62. Independent Schools Council. URL: http://www.iscis.org.uk. 2005.

63. OFSTED. URL: http://www.ofsted.gov.uk. 2005.

64. Rice DP, Cooper BS. The economic value of human life. *Am J Public Health* 1967;**57**:1954–66.

65. Matthews JNS, Altman D, Campbell D, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990;**300**:230–5.

66. Diggle PJ, Liang KY, Zeger SL. *Analysis of longitudinal data*. Oxford: Oxford Scientific Publications; 1994.

67. Crits-Christoph P, Mintz J. Implications of therapist effects for the design and analysis of comparative studies of psychotherapies. *J Consult Clin Psychol* 1991;**59**:20–6.

68. Roberts C. The implications of variation in outcome between health professionals for the design and analysis of randomized controlled trials. *Stat Med* 1999;**18**:2605–15.

69. Efron B, Tibshirani RJ. *An introduction to the bootstrap*. New York: Chapman and Hall; 1993.

70. Barber JA, Thompson SG. Analysis and interpretation of cost data in randomised control trials: review of published studies. *BMJ* 1998; **317**:1195–2000.

71. Van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and c/e-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.

72. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87.

73. Byford S, Barber JA, Harrington RC. Factors that influence the cost of deliberate self-poisoning in children and adolescents. *J Mental Health Policy Econ* 2001;**4**:113–21.

74. Barrett B, Byford S, Chitsabesan P, Kenning C. Mental health provision for young offenders: service use and cost. *Br J Psychiatry* 2006; **188**:541–6.

75. Byford S, Barber JA, Fiander M, Marshall S, Green J. Factors that influence the cost of caring for patients with severe psychotic illness: report from the UK700 trial. *Br J Psychiatry* 2001;**178**:441–7.

76. Harrington R, Whittaker J, Shoebridge P. Psychological treatment of depression in children and adolescents. A review of treatment research. *Br J Psychiatry* 1998;**173**:291–8.

77. Clarke G, Debar L, Lynch F, Powell J, Gale J, O'Connor E, *et al*. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *J Am Acad Child Adolesc Psychiatry* 2005;**44**:888–98.

78. March J, Silva S, Petrycki S, Curry J, Powell J, Gale J, *et al*. Fluoxetine, cognitive–behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA* 2004;**292**:807–20.

79. Curry J, Rhode P, Simons A, Silva S, Vitiello B, Kratochvil C, *et al*. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry* 2006;**45**:1427–39.

80. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A. Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;**363**:1341–5.

81. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. *BMJ* 2004;**328**:879–83.

82. Clarke GN, Hornbrook M, Lynch F, Polen M, Gale J, O'Connor E, *et al*. Group cognitive–behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:305–13.

83. Paykel ES. Cognitive therapy in relapse prevention in depression. *Int J Neuropsychopharmacol* 2007; **10**:131–6.

84. Goodyer IM, Herbert J, Tamplin A, Secher SM, Pearson J. Short-term outcome of major depression: II. Life events, family dysfunction, and friendship difficulties as predictors of persistent disorder. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:474–80.

85. Park RJ, Goodyer IM, Teasdale JD. Self-devaluative dysphoric experience and the prediction of persistent first-episode major depressive disorder in adolescents. *Psychol Med* 2005;**35**: 539–48.

86. Wilkinson PO, Goodyer IM. The effects of cognitive-behavioural therapy on mood-related ruminative response style in depressed adolescents. *Child Adolesc Psychiatry Ment Health* 2008;**2**:3.

87. Byford S, Barrett B, Roberts C, Wilkinson P, Dubicka B, Kelvin RG, *et al*. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. *Br J Psychiatry* 2007;**191**: 521–7.

88. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, *et al*. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA* 2008;**299**: 901–13.

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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