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Abstract

Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia (ACTIONS): a double-blind, placebo-controlled, randomised clinical trial

Thomas RE Barnes,[1,2]* Verity C Leeson,[1] Carol Paton,[1,3] Céire Costelloe,[4] Judit Simon,[5] Noemi Kiss,[5] David Osborn,[6,7] Helen Killaspy,[6,7] Tom KJ Craig,[8] Shôn Lewis,[9] Patrick Keown,[10] Shajahan Ismail,[11] Mike Crawford,[1] David Baldwin,[12] Glyn Lewis,[6,7] John Geddes,[13] Manoj Kumar,[14] Rudresh Pathak[15] and Simon Taylor[16]

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Background: Negative symptoms of schizophrenia represent deficiencies in emotional responsiveness, motivation, socialisation, speech and movement. When persistent, they are held to account for much of the poor functional outcomes associated with schizophrenia. There are currently no approved pharmacological treatments. While the available evidence suggests that a combination of antipsychotic and antidepressant medication may be effective in treating negative symptoms, it is too limited to allow any firm conclusions.

Objective: To establish the clinical effectiveness and cost-effectiveness of augmentation of antipsychotic medication with the antidepressant citalopram for the management of negative symptoms in schizophrenia.

Design: A multicentre, double-blind, individually randomised, placebo-controlled trial with 12-month follow-up.

Setting: Adult psychiatric services, treating people with schizophrenia.

Participants: Inpatients or outpatients with schizophrenia, on continuing, stable antipsychotic medication, with persistent negative symptoms at a criterion level of severity.

Interventions: Eligible participants were randomised 1 : 1 to treatment with either placebo (one capsule) or 20 mg of citalopram per day for 48 weeks, with the clinical option at 4 weeks to increase the daily dosage to 40 mg of citalopram or two placebo capsules for the remainder of the study.

Main outcome measures: The primary outcomes were quality of life measured at 12 and 48 weeks assessed using the Heinrich's Quality of Life Scale, and negative symptoms at 12 weeks measured on the negative symptom subscale of the Positive and Negative Syndrome Scale.

Results: No therapeutic benefit in terms of improvement in quality of life or negative symptoms was detected for citalopram over 12 weeks or at 48 weeks, but secondary analysis suggested modest improvement in the negative symptom domain, avolition/amotivation, at 12 weeks (mean difference –1.3, 95% confidence interval –2.5 to –0.09). There were no statistically significant differences between the two treatment arms over 48-week follow-up in either the health economics outcomes or costs, and no differences in the frequency or severity of adverse effects, including corrected QT interval prolongation.

Limitations: The trial under-recruited, partly because cardiac safety concerns about citalopram were raised, with the 62 participants recruited falling well short of the target recruitment of 358. Although this was the largest sample randomised to citalopram in a randomised controlled trial of antidepressant augmentation for negative symptoms of schizophrenia and had the longest follow-up, the power of statistical analysis to detect significant differences between the active and placebo groups was limited.

Conclusion: Although adjunctive citalopram did not improve negative symptoms overall, there was evidence of some positive effect on avolition/amotivation, recognised as a critical barrier to psychosocial rehabilitation and achieving better social and community functional outcomes. Comprehensive assessment of side-effect burden did not identify any serious safety or tolerability issues. The addition of citalopram as a long-term prescribing strategy for the treatment of negative symptoms may merit further investigation in larger studies.

Future work: Further studies of the viability of adjunctive antidepressant treatment for negative symptoms in schizophrenia should include appropriate safety monitoring and use rating scales that allow for evaluation of avolition/amotivation as a discrete negative symptom domain. Overcoming the barriers to recruiting an adequate sample size will remain a challenge.

Trial registration: European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2009-009235-30 and Current Controlled Trials ISRCTN42305247.

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List of abbreviations

5-HT	5-hydroxytryptamine (serotonin)
ACTIONS	Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia
ANNSERS	Antipsychotic Non-Neurological Side Effects Scale
ANNSERS-c	compiled Antipsychotic Non-Neurological Side Effects Scale
CDSS	Calgary Depression Rating Scale for Schizophrenia
CI	confidence interval
CUtLASS 1	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CYP	cytochrome P450
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition
ECG	electrocardiogram
EQ-5D-3L	European Quality of Life-5 Dimensions, 3 Levels
FDA	Food and Drug Administration
ICECAP-A	ICEpop CAPability measure for Adults
MHRA	Medicines and Healthcare products Regulatory Agency
PANSS	Positive and Negative Syndrome Scale
QLS	Quality of Life Scale
QTc	corrected QT
RCT	randomised controlled trial
REC	Research Ethics Committee
SD	standard deviation
SSRI	selective serotonin reuptake inhibitor

Plain English summary

Schizophrenia affects behaviour, thinking and perception and, when more severe, the ability to socialise, work and carry out routine daily tasks. In addition to the well-known 'positive' symptoms such as false beliefs ('delusions') and hallucinations (most commonly, hearing voices), the illness can have 'negative' symptoms: some loss of a person's drive and the usual emotional expressiveness and responsiveness.

If negative symptoms persist despite adequate treatment with antipsychotic medication, there are no other medications that we know can help. However, adding antidepressant medication might reduce negative symptoms and not produce too many side effects.

In this study, we assessed symptoms and side effects over the course of a year in people with schizophrenia, randomly assigned to treatment with either an antidepressant (citalopram) or an identical dummy tablet (placebo). None of the participants or any of the people assessing how the illness was responding over time knew who was receiving which medication. This allowed us to carry out an unbiased comparison of the two treatments at the end of the study. We found no significant differences between citalopram and placebo in side effects or effects on quality of life or negative symptoms, although it may have helped to improve drive and motivation, at least in the first 3 months. Further studies with larger numbers of patients are needed to really test the value of this treatment, as we were only able to recruit 62 out of 358 participants and so may have missed meaningful differences between those taking citalopram and those taking placebo.

Scientific summary

Background

The negative symptoms of schizophrenia represent deficiencies in emotional responsiveness, motivation, socialisation, speech and movement. Two subdomains are recognised: expressive deficits (including symptoms of affective flattening and poverty of speech) and avolition/amotivation for daily life and social activities (including apathy, amotivation and asociality). For people with schizophrenia, persistent negative symptoms are held to account for a disproportionate degree of long-term morbidity and poor functional outcome. The notion that adding an antidepressant to continuing antipsychotic medication may treat negative symptoms has been mooted for almost 20 years. Reviews of the relevant, randomised controlled trials of adjunctive antidepressant treatment have concluded that the combination of antipsychotics and antidepressants may be effective in treating the negative symptoms of schizophrenia, but the amount and quality of the evidence available is too limited to allow for any robust conclusion about the potential risks and benefits of such a strategy.

Objective

The aim was to establish the clinical effectiveness and cost-effectiveness of the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram as an adjunct to continuing antipsychotic medication in the management of persistent negative symptoms of schizophrenia.

Design

The Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia (ACTIONS) was a multicentre, double-blind, individually randomised, placebo-controlled, parallel-arm randomised controlled trial (RCT) with 12-month follow-up.

Setting

Adult psychiatry NHS multidisciplinary teams, treating people with schizophrenia as either inpatients or outpatients.

Participants

People with an established diagnosis of schizophrenia, maintained on a stable regimen of antipsychotic medication and who had persistent negative symptoms at a criterion level of severity. The sample size calculation yielded a target recruitment of 358 individuals.

Interventions

Eligible participants were randomised 1 : 1 to treatment with either placebo (one capsule) or 20 mg of citalopram per day for 48 weeks, but with the clinical option at 4 weeks to increase the daily dose to 40 mg of citalopram or two placebo capsules for the remainder of the study.

Outcome measures

The primary outcomes were quality of life measured at 12 and 48 weeks, assessed using an observer-rated scale – the Heinrich's Quality of Life Scale – and negative symptoms, measured on the negative symptom subscale of the Positive and Negative Syndrome Scale as well as subscales derived to assess the 'expressive deficits' and 'avolition/amotivation' sub-domains. Secondary outcome measures included ratings of depression in schizophrenia, social functioning and adherence to the study medication. Medication side effects were systematically investigated, including electrocardiogram measurements and the use of rating scales designed to comprehensively assess the adverse effects of second-generation antipsychotics and SSRI antidepressants. In addition, a range of health economic outcomes was measured.

Results

Sixty-two participants were randomised between September 2011 and the end of September 2013. No therapeutic advantage was detected for adjunctive citalopram over 12 weeks or at 48 weeks in terms of improvement in quality of life or negative symptoms, except for modest improvement in the avolition/amotivation negative symptom domain at 12 weeks (mean difference –1.3, 95% confidence interval –2.5 to –0.09). There were no statistically significant differences between the two treatment arms over the 48-week follow-up period in either the health economics outcomes or costs. There was no difference between the two treatment groups in the duration of the corrected QT interval over the follow-up period and no difference in the frequency or severity of adverse effects.

Limitations

The trial under-recruited, partly because cardiac safety concerns about citalopram were raised and partly because of the difficulties in engaging clinical teams. Although it had the longest follow-up period and the largest number of people randomised to citalopram of any RCT of antidepressant augmentation for negative symptoms of schizophrenia conducted thus far, the final sample size fell well short of the target recruitment of 358 participants. The power of any statistical analysis to detect clinically or statistically meaningful significant differences between the citalopram and placebo groups was, therefore, limited. A range of barriers was encountered to recruiting participants; the hurdles of research governance, regulation and NHS permissions, contracts and costs allocation delayed the opening of the study sites. Furthermore, referrals to the study were necessarily via a member of a patient's clinical team, and clinical teams had competing clinical priorities, concerns about how introducing a trial to a patient might impact on their therapeutic relationship and a lack of understanding of the clinical equipoise of the research question. In addition, clinicians had safety concerns regarding the trial medication regimen of citalopram added to antipsychotic medication, given the Medicines and Healthcare products Regulatory Agency warning in 2011 about the risk of corrected QT interval prolongation with citalopram, which contraindicated such a combination, and the consequent need to implement urgent safety measures in the study.

Conclusions

There is the suggestion from the study findings that citalopram can have a positive effect on avolition/amotivation, at least in the short term, which is recognised as a critical barrier to psychosocial rehabilitation and to achieving better social and community functional outcomes. In addition, comprehensive assessment of side-effect burden did not identify any serious safety or tolerability issues for citalopram as an adjunct to continuing antipsychotic medication. Further investigation of the viability and risk–benefit of long-term adjunctive antidepressant treatment as a prescribing strategy for the treatment of negative symptoms in schizophrenia may be warranted.

Future research

Future studies of adjunctive antidepressant treatment for negative symptoms in schizophrenia should include appropriate safety monitoring and use rating scales that allow for evaluation of avolition/amotivation as a discrete negative symptom domain. Overcoming the barriers to recruiting an adequate sample size will remain a challenge for trials conducted in a similar clinical setting to ACTIONS.

Trial registration

This trial is registered as ISRCTN42305247.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Negative symptoms of schizophrenia

The negative symptoms of schizophrenia represent an important dimension of psychopathology and reflect the absence or diminution of normal behaviours and functions. They include deficiencies in emotional responsiveness (blunted or flat affect), poverty of speech, poor rapport, emotional and social withdrawal, anhedonia, apathy and avolition. Such phenomena have been recognised as part of a schizophrenic illness since early in the last century. Kraepelin[1] described the more severe dissolution of personality seen in some people with schizophrenia, referring to 'weakening of those emotional activities which permanently form the mainspring of volition' (p. 74), with the process resulting in 'emotional dullness, failure of mental activity, loss of mastery over volition, of endeavour, and of ability for independent action' (p. 75). Bleuler[2] noted that some patients 'appear lazy and negligent because they no longer have the urge to do anything either of their own initiative or at the bidding of another' (p. 70).

The introduction of antipsychotic medication in the 1950s revolutionised the treatment of schizophrenia. But the efficacy of these drugs in alleviating the positive symptoms of this illness tended to focus attention on such symptoms as the main treatment target, and it was not until 25 years or so later that attention once again turned to the role of negative or deficit symptoms. Studies have consistently reported worse functional outcomes in individuals with more prominent negative symptoms,[3–5] demonstrating correlations between negative symptoms and impairments in occupational and social functioning in the community, as well as a reduced likelihood of living independently.[6,7] Cognitive dysfunction has also been repeatedly demonstrated to contribute to poor functional outcomes in schizophrenia.[8,9] While a degree of overlap between cognitive dysfunction and negative symptoms has been identified,[10] they are generally conceptualised as separate domains.[11]

Persistent negative symptoms are held to account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia. In this regard, an important clinical distinction is between primary negative symptoms, which comprise an enduring deficit state, predict a poor prognosis and are stable over time, and secondary negative symptoms, which are consequent upon positive psychotic symptoms, depression or demoralisation, or medication side effects, such as bradykinesia as part of drug-induced parkinsonism. Secondary negative symptoms tend to be more common during acute psychotic episodes and would be expected to respond to treatment of the underlying cause. Around half to three-quarters of people with chronic schizophrenia objectively exhibit some negative symptoms,[12] although the figure for persistent, primary negative symptoms is probably 15–20%.[13,14]

While most research on negative symptoms assumes they constitute a single syndrome or therapeutic target, factor analysis has consistently generated two distinct domains.[15] The first may be conceptualised as expressive deficits: this comprises 'alogia' as a decrease in verbal output or verbal expressiveness and 'flattened or blunted affect' assessed by diminished facial emotional expression, poor eye contact, decreased spontaneous movement and lack of spontaneity. The second may be characterised as avolition/amotivation for daily life and social activities: this comprises 'avolition' as a subjective reduction in interests, desires and goals, and a behavioural reduction of self-initiated and purposeful acts, and 'asociality', manifest as a lack of self-initiated social interactions. Some would include 'anhedonia' in this domain. Anhedonia has been considered to reflect a diminished capacity for pleasure in all psychiatric and neurological conditions in which it is manifest, but recent, plausible arguments suggest that in schizophrenia it may reflect complex, abnormal psychological processes, such as low-pleasure beliefs and a reduction in the normal tendency to overestimate past and future pleasure, as well as dysfunctional behavioural processes such as reduced pleasure-seeking behaviour.[16,17] Cognitive impairments may play a role in these psychological and behavioural components of anhedonia.

Pharmacological treatment of negative symptoms

The introduction of the second-generation antipsychotics was accompanied by claims that even primary negative symptoms might respond to this new group of antipsychotics, but evidence for an effect independent of an improvement in positive symptoms or medication side effects remains limited,[18,19] and recent effectiveness data[20,21] provide little support for a robust effect in this regard, with the possible exception of clozapine.[22–24]

Antipsychotic medications aside, there are currently no approved pharmacological treatments for negative symptoms of schizophrenia. A range of potential pharmacological interventions has been tested in small studies, usually as augmentation of antipsychotic medication. The drugs used include antidepressants, principally selective serotonin reuptake inhibitors (SSRIs) and mirtazapine,[25,26] dehydroepiandrosterone, selegiline hydrochloride (a selective monoamine oxidase inhibitor), cholinesterase inhibitors, omega-3 fatty acids[27] and *Ginkgo biloba* extracts. In addition, a range of glutamatergic agents has been tried, such as glycine, D-cycloserine and glutathione, as well as alpha-7 nicotinic agonists, modulators of metabotropic glutamate receptors, and minocycline – an antibiotic that may exert differential control over NMDA (*N*-methyl-D-aspartate) receptor signalling.

Prevalence of the use of antidepressants with antipsychotics in schizophrenia

In current clinical practice, antidepressants are commonly used in combination with antipsychotics. For example, audit data from the UK Prescribing Observatory for Mental Health revealed that of 3885 community patients with schizophrenia or related disorder (*International Classification of Diseases*, Tenth Revision,[28] diagnostic category F20–29) who were prescribed depot/long-acting antipsychotic injections in the community, 640 (16.5%) were also prescribed an antidepressant.[29] Furthermore, of 1502 patients in the same diagnostic category under the care of forensic services, 287 (19%) were also prescribed an antidepressant.[30] The clinical indications for such a combination are likely to be comorbid depression or negative symptoms, but the magnitude of use specifically to treat the latter is not known.

Efficacy of antidepressant augmentation for negative symptoms

Currently available treatments for negative symptoms have only modest benefits, with the result that negative symptoms continue to disproportionately limit patient recovery.[19,31,32] The notion that adjunctive antidepressant medication may treat the negative symptoms of schizophrenia has been mooted for almost 20 years.[33–35] Clinical trials have provided evidence that the combined administration of an antipsychotic drug and an 'add-on' SSRI – such as fluoxetine, fluvoxamine, paroxetine or citalopram – can improve negative symptoms and some affective disorders associated with schizophrenia, without exacerbating extrapyramidal side effects, in patients in whom such problems have proved persistent and who have been, being unresponsive to antipsychotic monotherapy.[36–41] For example, the efficacy and safety of paroxetine augmentation has been demonstrated in small pilot studies[42] and a double-blind placebo-controlled study.[41] Fluvoxamine and fluoxetine have also shown some beneficial effects in placebo-controlled, double-blind studies,[36,38,43] in particular, fluvoxamine improved affective blunting. Fluoxetine in combination with a depot antipsychotic caused an overall improvement in negative symptoms,[38] although it failed to do so in combination with clozapine.[31]

Such benefit may not be limited to SSRI antidepressants: one double-blind, placebo-controlled trial tested the augmentation of clozapine with mirtazapine (which has antagonist properties at serotonin receptors 5-HT2A, 5-HT3 and alpha-2 adrenergic receptors as well as an indirect 5-HT1A agonist effect) for the treatment of negative symptoms of schizophrenia.[44] A significant reduction in negative symptom scores in

the mirtazapine group was reported, with a significant improvement on the avolition/apathy and anhedonia/asociality subscales of the Scale for the Assessment of Negative Symptoms. Zocalli *et al.*[45] considered that there was a potential role for mirtazapine as an augmentation strategy in the treatment of negative symptoms of schizophrenia, without negative effects on the metabolism of different antipsychotics. Berk *et al.*[46] conducted a 6-week, randomised, placebo-controlled trial of mirtazapine added to haloperidol in a sample of inpatients with schizophrenia. Negative symptom scores were again significantly reduced in the mirtazapine group compared with the placebo group by the end of the trial period. The lack of any difference between the treatment groups on depression ratings led the investigators to conclude that the improvement in negative symptoms was not an artefact of mood improvement. Having conducted a meta-analysis of data from five placebo-controlled double-blind randomised controlled trials (RCTs) of mirtazapine, including the Berk *et al.*[46] study, Vidal *et al.*[47] concluded that the findings supported the hypothesis that mirtazapine augmentation of antipsychotic medication could improve negative symptoms in schizophrenia, but considered that additional and larger studies, with more methodological rigour, were needed.

In another double-blind, placebo-controlled study, Shoja-Shafti[48] reported that augmentation of haloperidol with the antidepressant nortriptyline, a serotonin and noradrenaline reuptake inhibitor with anticholinergic effects, produced a significant reduction in negative symptom scores. However, there is some evidence that adding a noradrenaline reuptake inhibitor (e.g. maprotiline) antidepressant to an antipsychotic may not improve schizophrenic negative symptoms.[49]

The mechanism by which adding an antidepressant to antipsychotic medication may cause a reduction in negative symptoms is unclear. The explanations postulated have included a non-specific antidepressant effect, generally increased noradrenergic drive and, more specifically, alpha-2 antagonism. How serotonergic agents might specifically exert any such benefit also remains unknown,[50] not least because both SSRI antidepressants and 5-HT2 antagonists (most second-generation antipsychotics) have claims for improving negative symptoms in schizophrenia.[51] Nevertheless, the clinical evidence has been enough to prompt investment in the development of novel antipsychotic drugs that selectively combine SSRI functionality with D2 dopamine receptor antagonism.[52] However, it is possible that SSRI effectiveness might be influenced by the pharmacological action of the antipsychotic medication.

Systematic reviews focusing on the effects of the combination of antipsychotic and antidepressant drug treatment for the management of negative symptoms have been relatively circumspect in their conclusions, partly reflecting that most of the relevant studies have been characterised by small sample sizes and failure to control for change in secondary negative symptoms of schizophrenia. Rummel *et al.*[53] reviewed five eligible RCTs testing the combination of an antidepressant (amitriptyline, mianserin hydrochloride, trazodone hydrochloride, paroxetine, fluoxetine or fluvoxamine) added to antipsychotic medication against an antipsychotic alone for the treatment of prominent negative symptoms in schizophrenia and/or schizophrenia-like psychoses. Significant differences in favour of the combination therapy were seen in core negative symptoms: affective flattening, alogia and avolition.

Sepehry *et al.*[54] conducted a further meta-analysis of 11 randomised, placebo-controlled, double-blind trials (five involving fluoxetine, two involving sertraline, two involving fluvoxamine, one involving paroxetine and one involving citalopram) specifically comparing the addition of SSRI antidepressants to antipsychotics versus adding placebo for negative symptoms in people with schizophrenia spectrum disorder. They included studies excluded by Rummel *et al.*[53] on methodological grounds, for example, where the study sample was not characterised by predominant negative symptoms. The total sample size for the 11 studies was still relatively small (393 patients). Sepehry *et al.*[54] concluded that the findings of the trials, which lasted between 4 and 16 weeks, provided no global support for the addition of a SSRI for the treatment of negative symptoms of schizophrenia, which had shown a poor response to antipsychotics alone, although a mild therapeutic effect could exist in patients with more 'chronic' illness. Lecrubier *et al.*[55] commented that these results suggested that a treatment period longer than 1–3 months may be needed before there is substantial benefit, and considered that the conclusion should not be extrapolated to all people with schizophrenia.

A subsequent meta-analysis by Singh *et al.*[56] included data from 23 randomised, placebo-controlled trials comparing the effect of antidepressants and placebo on the negative symptoms of chronic schizophrenia. These investigators concluded that antidepressants prescribed along with antipsychotics were more effective in treating the negative symptoms of schizophrenia than antipsychotics alone. They reported a small-to-medium effect size (−0.48; $p < 0.05$), comparable with a later meta-analysis of 26 relevant RCTs by Fusar-Poli *et al.*[57] which yielded similar, respective figures (−0.349; $p = 0.001$). Nevertheless, a Cochrane review,[58] although agreeing that a combination of antipsychotics and antidepressants may be effective in treating negative symptoms of schizophrenia, considered that the research information available was currently too limited to allow any firm conclusions to be drawn, and that large, pragmatic, well-designed and well-reported long-term trials were justified.

Selection of an antidepressant for augmentation

The question investigated in this study was whether or not antidepressants benefit negative symptoms in schizophrenia independent of any beneficial impact on depressive symptoms. For that reason, we excluded people who had a definite comorbid depressive illness. Although there is some controlled evidence that antidepressants are useful in treating depression when this fulfils DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition[59]) criteria for major depressive disorder superimposed on schizophrenia,[60] the use of a combination of an antidepressant and antipsychotic agent has not been found universally helpful for depression occurring in the course of schizophrenia.[61–63] Glick *et al.*[64] suggested that such adjunctive medication is not generally helpful in established schizophrenia for depressive features, as they usually represent demoralisation. However, antidepressants are widely used and if people with depression had been included this could have reduced the acceptability of the randomisation to placebo or antidepressant, and potentially confused the picture. Similar reasoning argued for using an antidepressant medication that did not have any anticholinergic activity. Such activity could ameliorate extrapyramidal symptoms and so lead to a spurious, apparently beneficial effect on negative symptoms. These considerations, along with other considerations given below, guided the selection of a SSRI antidepressant for testing in this study.

When adding one drug to another it is important to consider any potential for interactions that could lead to adverse consequences for the patient. Drug interactions can be either pharmacokinetic (where one drug interferes with the way the body handles the other, usually by increasing or decreasing metabolism of the day) or pharmacodynamic (where one drug enhances or opposes the pharmacological action of the other). When added to an antipsychotic, almost all antidepressant drugs can precipitate at least one of these types of interaction and patients may experience an increased side-effect burden as a result.

With respect to pharmacokinetic interactions, for example, the SSRI antidepressants fluoxetine and paroxetine are both potent inhibitors of the hepatic cytochrome P450 (CYP) enzymes CYP2D6 and 3A4, which metabolise many antipsychotic drugs, most notably clozapine. When such enzyme activity is inhibited, the capacity to metabolise clozapine is significantly reduced and this can result in the patient experiencing serious clozapine-related side effects, such as seizures.[42,65,66]

With respect to pharmacodynamic interactions, most antipsychotic drugs have variable affinity for Histamine H1, alpha-1-adrenergic and acetylcholine receptors leading, to side effects such as sedation, postural hypotension and constipation, respectively.[66] Tricyclic antidepressants also have affinity for these receptors and, for example, when combined with risperidone would be predicted to exacerbate postural hypotension, or when combined with olanzapine, sedation and constipation. Unacceptable side effects are an important cause of non-adherence to prescribed medication.[67]

Considering the choice of augmenting antidepressant, among the SSRIs no individual agent has a convincingly stronger evidence base for treating negative symptoms[54,58] and therefore safety and pharmacokinetic considerations are key. As discussed above, some SSRIs are potent inhibitors of the hepatic CYP enzymes involved in the metabolism of certain antipsychotics, leading to variable increases in plasma antipsychotic drug concentrations. Of particular concern is that some patients with enduring negative symptoms are likely to be receiving clozapine; increases in clozapine plasma levels are associated with potentially serious side effects such as seizures and serotonergic syndrome.[42,65] The risk of a pharmacokinetic interaction is lowest with the SSRI citalopram. At the time the Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia (ACTIONS) began, the only published evidence for citalopram as an adjuvant treatment in patients with established schizophrenia and persistent negative symptoms[39] was positive, being associated with a significant advantage over placebo on 'subjective well-being'.

As the patients recruited to our study could be receiving any antipsychotic drug, it was important to select an augmenting antidepressant that was both well tolerated and had minimal potential to interact with any antipsychotic in any way. Citalopram best fits these criteria, being generally well tolerated, having little effect on hepatic metabolising enzymes and having a relatively low affinity for alpha-1-adrenergic and muscarinic receptors.[66]

Study aims

The main objectives were, first, to test the benefits of citalopram (a SSRI antidepressant) for people with schizophrenia and negative symptoms in terms of improved quality of life and reduction of negative symptoms, as well as recording the relative risks and costs of this augmentation of antipsychotic medication. Second, the study was designed to extend the current evidence that indicates that SSRI augmentation in the treatment of schizophrenia acts directly on negative symptoms, has only limited efficacy in treating depressive symptoms, and does not have a detrimental effect on positive symptoms or extrapyramidal side effects.

Chapter 2 Methods

Trial design

The study was a multicentre, double-blind, individually randomised, placebo-controlled, parallel-arm RCT with a 1-year follow-up. Following the baseline assessment, follow-up assessments occurred after 12, 36 and 48 weeks. The first participant was recruited in September 2011 and recruitment finished at the end of September 2013.

Sample size

Calculation of the target sample size used the pragmatic, Health Technology Assessment-funded Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) of first- versus second-generation antipsychotic treatment for broadly defined, treatment-resistant schizophrenia[21,68] as a precedent. In CUtLASS 1, the within-group standard deviation (SD) for the Heinrich's Quality of Life Scale[69,70] (QLS) change score at 12 months was 13. There is often difficulty in defining a clinically significant difference in scores. There is some justification for considering a difference of over 4.5 points or 0.35 SDs as an important change,[71,72] which is slightly less than the CUtLASS 1 assumption of a 5-point increase being the criterion for a clinically important improvement. In order to detect a difference of 0.35 SDs with 85% power at 5% significance (two-sided), data on 148 individuals in each group were required. In CUtLASS 1 there was 83% follow-up at 3 and 12 months; assuming the same attrition as CUtLASS 1, the recruitment target was 358 individuals. The same calculations would also apply to scores on the Positive and Negative Syndrome Scale (PANSS), the other primary outcome. In CUtLASS 1 the SD for the PANSS negative subscale was 6, so 0.35 SDs would correspond to approximately 2 points.

Primary outcomes

The primary outcome was quality of life measured at 12 and 48 weeks, assessed using an observer-rated scale, the QLS,[69] and negative symptoms at 12 weeks, measured on the negative symptoms subscale of the PANSS.[73] We also used the PANSS negative symptom subscale revised by Marder *et al.*,[74] which consists of the following PANSS items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, motor retardation, active social avoidance and lack of spontaneity/flow of conversation. Furthermore, we derived assessments for the two distinct domains of negative symptom psychopathology,[15,75,76] 'expressive deficits' and 'avolition for daily life and social activities', as separable components of the negative syndrome that might have a differential response to treatment interventions.[77] Two subscales were generated: an expressive deficits subscale (comprising three PANSS items: lack of spontaneity and flow of conversation, poor rapport and blunted affect) and an avolition subscale (comprising three PANSS items: disturbance of volition, emotional withdrawal and passive/apathetic emotional withdrawal). These subscales are composed of items also included in the two respective subdomains of negative symptoms ('expressive deficits' and 'social amotivation') yielded by an exploratory factor analysis of PANSS items by Liemburg *et al.*[78]

Secondary outcomes

Mental state symptoms were assessed using the PANSS total and positive symptoms subscale.[73] Depression was assessed using the Calgary Depression Rating Scale for Schizophrenia (CDSS).[79] Social function was assessed by the Birchwood Social Function Scale[80] and the level of engagement with clinical services by the Service Engagement Scale.[81] Antipsychotic side effects were assessed comprehensively by a combination of scales. General side effects were systematically evaluated using the Antipsychotic Non-Neurological Side Effects Scale (ANNSERS),[82] which covers a range of aversive subjective experiences as well the cardiovascular, gastrointestinal, endocrine/metabolic, autonomic, genitourinary, sexual and central nervous system side effects of antipsychotic medication. Additional items were added to address recognised SSRI antidepressant side effects, including serotonergic symptoms, such as nausea and dizziness. These additional SSRI antidepressant side effect items were collated as the ANNSERS-compiled (ANNSERS-c) rating scale. The motor, extrapyramidal side effects were rated with scales for each of the distinct motor syndromes: drug-induced parkinsonism was rated using the Extrapyramidal Side Effects Scale,[83,84] akathisia using the Barnes Akathisia Rating Scale[85] and tardive dyskinesia using the Abnormal Involuntary Movements Scale.[86] Medication adherence was tested using the self-reported Morisky Compliance scale.[71]

In addition, there was a range of health economic outcome measures. In line with the recommendations from the National Institute for Health and Care Excellence,[87] the European Quality of Life-5 Dimensions, a widely used, generic, multiattribute utility scale, was completed for each participant at baseline, 12, 36 and 48 weeks, to measure patients' general health-related quality of life.[88] A new measure of capabilities, the ICEpop CAPability measure for Adults (ICECAP-A),[89] was also used alongside this as it was anticipated that this measure would become an important outcome measure for economic analysis by the end of the trial. The capability approach is a fairly new concept that defines well-being in terms of an individual's ability to 'do' and 'be' the things that are important in life. It provides a broader framework for benefit measure in economic evaluations than the current gold standard, health-related quality of life. In addition, a short specific questionnaire was also completed to collect resource-use information in the trial from a social perspective.

Protocol changes

In addition to wording changes to clarify procedures, a number of amendments were made to the protocol during the trial, as described in the following sections.

The addition of study sites

Additional sites were added as the trial progressed, which increased the total number of study sites from 7 to 15.

Changes to the planned assessments

The Mini Mental State Examination was replaced with a short cognitive test battery to measure general cognition. A measure of capabilities, the ICECAP-A, to be completed by the participant and a measure of completion by the carer were added. These changes were implemented prior to randomisation of the first participant.

Urgent safety measures

On 24 October 2011, Lundbeck Limited in collaboration with the Medicines and Healthcare products Regulatory Agency (MHRA) issued a letter[99] to inform health-care professionals in the UK of new recommendations for the use of citalopram. These were based on the findings of an unpublished, randomised, multicentre, double-blind, placebo-controlled crossover study of the cardiac effects of citalopram involving 119 healthy non-depressed participants.[90–93] The letter referred to revision of the product information to include the following:

> *Citalopram is now contraindicated in patients with known QT interval prolongation on ECG [electrocardiogram] or congenital long QT syndrome. Co-administration with another medicinal product that can prolong the QT interval is also contraindicated.*
>
> *MHRA*[99]

Following discussion with the MHRA and ethics committee, the trial continued with implementation of urgent safety measures: amendment to the wording of exclusion criterion 2 (see *Exclusion criteria*), and the addition of exclusion criteria 3 and 4. Furthermore, to be eligible for the study a patient should not be receiving a drug that prolongs the QT interval (other than an antipsychotic, excluding pimozide) or significantly interferes with the metabolism of such a drug; the patient's consultant must confirm that they are not known to have QT interval prolongation, a congenital long-QT syndrome, congestive heart failure or bradyarrhythmias; a patient's serum potassium and/or magnesium levels must not be below the lower limits of normal (according to a blood test in the last 3 months).

However, these changes were not approved by the Research Ethics Committee (REC) when submitted as a substantial amendment. The REC made alternative recommendations that were not considered appropriate by the MHRA and therefore obtaining global approval was delayed. No further participants could be randomised while the case was being considered by an appeal REC. After 7 months of negotiations and intervention by the Head of Operation at the Health Research Authority, REC approval was given for the urgent safety measures with the additional introduction of hand-held ECG machines to screen participants for prolonged corrected QT interval (QTc) prior to study entry, and for monitoring at each follow-up. In accordance with MHRA guidelines, participants were excluded if QTc was > 450 milliseconds pre-randomisation, and withdrawn from the study if the QTc duration had increased to either > 500 milliseconds or if QTc duration at any follow-up assessment was > 60 milliseconds greater than that recorded pre randomisation.

Payment of participants for study assessments

In line with a number of contemporaneous studies that were remunerating participants for their time, a payment to participants of £20 for each assessment was introduced in recognition of any expenses incurred (e.g. travel) and inconvenience. This was backdated for any participants who were already randomised.

Participants

The study was conducted at 15 clinical sites in the UK. The first participant was recruited in September 2011 and recruitment finished at the end of September 2013. The participants were people under the care of secondary mental health services, with an established schizophrenic illness characterised by persistent negative symptoms at a criterion level of severity, despite treatment with antipsychotic medication: a negative subscale score of 20 or more[41,94,95] on the PANSS with at least three of the seven items on the negative symptom subscale rated ≥ 3. Eligibility for the study was determined by the following, additional, inclusion and exclusion criteria.

Inclusion criteria

1. An Operational Criteria Checklist for Psychosis[94,96] diagnosis of schizophrenia, schizophreniform, schizoaffective disorder or psychosis not otherwise specified, as defined by DSM-IV.
2. Aged 18–65 years, inclusive.
3. Clinically stable for the last 3 months with a consistent antipsychotic regimen.
4. Competent and willing to provide written, informed consent.

Exclusion criteria

1. Any medical contraindications to a SSRI antidepressant.
2. Taking any drug that risks interaction with citalopram, for example pimozide, monoamine oxidase inhibitors, metoprolol, St John's wort (*Hypericum perforatum*), lithium, tryptophan, anticonvulsants, insulin and other medicines for diabetes, anticoagulants, regular aspirin or non-steroidal anti-inflammatory drugs (such as ibuprofen), serotonergic drugs (such as tramadol and sumatriptan) including those that may prolong the QT interval (e.g. cimetidine, CYP3A4 and CYP2C19 inhibitors), except antipsychotics other than pimozide (Orap®, Janssen Pharmaceutica).

3. Known QT interval prolongation or congenital long-QT syndrome, congestive heart failure, bradyarrhythmias.
4. Serum potassium and/or magnesium levels below the lower limits of normal.
5. Currently receiving any antidepressant drug or current clinician wants to treat with an antidepressant.
6. Currently fulfil criteria for major depressive disorder, or alcohol/substance hazardous use or dependence in past 3 months.
7. Pregnant or planning to become pregnant.
8. Treated with electroconvulsive therapy in the last 8 weeks.
9. Cognitive or language difficulties that would preclude subjects providing informed consent or compromise participation in study procedures.
10. Lack of capacity, as judged by the patient's psychiatrist.

Pharmacological intervention

Eligible participants were randomised 1 : 1 to treatment with either placebo (one capsule) or 20 mg of citalopram per day for 48 weeks, but at 4 weeks a participant's clinician had the option to increase the dose of citalopram to 40 mg per day or two placebo capsules for the remainder of the study; if there were problems with tolerability the clinician could reduce the dose back to 20 mg per day (or one placebo capsule). Medication was supplied as identical capsules containing either 20 mg of citalopram or placebo, packaged into monthly packs of 28 tablets. The 20-mg dose or the starting placebo dose was prescribed as one capsule each morning; the 40-mg dose or increased placebo option was prescribed as two capsules each morning. Participation in the study did not restrict the therapeutic options of the clinical team in terms of additional medication (with the exception of additional mood stabilisers or other antidepressants, which were not allowed) or psychosocial interventions. A fully automated online (and telephone) randomisation service was provided by the Bristol Randomised Trials Collaboration. In addition, a 24-hour unblinding service was provided by the Medical Toxicology Information Service of Guy's and St Thomas' NHS Foundation Trust.

Patient and public involvement

During development of the application for funding, a North London, service-user led group dedicated to facilitating research (SUNLOWS) provided advice on the trial design. Both the Trial Management Group and Trial Steering Committee had a mental health service user as a member. In addition, this individual was involved in the development of documents for participants, such as the information sheet and newsletters.

Data analysis

The analysis and reporting of this trial were undertaken in accordance with Consolidated Standards of Reporting Trials guidelines.[97] All analyses were conducted in Stata 12.1 (StataCorp LP, College Station, TX, USA), following a pre-defined analysis plan agreed with the Trial Steering Committee. All program files were stored to maintain a record of any generated variables and analyses, along with a copy of the regional data set. All analyses remained blind to the intervention group until they were completed.

Descriptive statistics of the key clinical and sociodemographic variables were used to review the data. The baseline comparability of the intervention and control groups was examined in terms of QLS and PANSS negative subscale score. These and other potential prognostic factors were examined over the course of the study, including PANSS total score, CDSS score, Birchwood Social Function Scale score, Service Engagement Scale score, ANNSERS total score, the scores on the extrapyramidal side effects rating scales and medication adherence. In addition, health and social care resource use and sociodemographic information were compared between the two groups.

Baseline data are reported for the intervention and control group. The data are presented in tables with mean and SDs for continuous outcome measures, and proportions and range for binary outcomes. For the primary outcome, linear regression was used to determine mean difference between treatment groups. Differences between groups are presented as mean differences with associated 95% confidence interval (CI). Baseline values for variables were included as covariates in regression models and adjusted according to analysis of covariance. All analyses were conducted under the intention-to-treat principle.

Health economic analysis

An economic analysis was conducted alongside the clinical trial to explore the cost-effectiveness of administering antidepressants in combination with antipsychotics to treat the negative symptoms of schizophrenia in patients who do not fulfil the criteria for major depressive disorder. The economic evaluation was a prospectively designed analysis, primarily from a health and social care perspective and secondarily from a societal perspective. The study was to be a within-trial cost–utility analysis to explore the incremental cost per quality-adjusted life-year gained from the additional SSRI treatment of patients with schizophrenia over 48 weeks.

During the clinical trial, health economics data were collected at baseline, 12, 36 and 48 weeks. The primary health economics outcome was the European Quality of Life-5 Dimensions, 3 Levels (EQ-5D-3L), in line with recommendations from the National Institute for Health and Clinical Excellence.[98] The EQ-5D-3L is a generic multiattribute utility scale, including two dimensions (usual activities, anxiety/depression) that are likely to be sensitive to possible changes occurring in the negative symptoms of these participants specifically.[88] Furthermore, ICECAP-A was used to further explore patients' capabilities, addressing well-being from a broader angle including an individual's ability to 'do' and 'be' the things that are important in life.[89]

A short, specific questionnaire was designed and piloted to collect resource-use information in the trial from a societal perspective. The questionnaire covered all health and social services use related to the disease, the intervention and its potential side effects. Resource use was thus measured on a patient level and utilisation was categorised as psychiatric medication (trial and non-trial), mental health inpatient and outpatient, non-mental health inpatient and outpatient, primary social care and informal care utilisation. Additionally, absenteeism was measured in those who were employed; and information on accommodation was also solicited. The use of health and social care services and indirect costs were collected by self-report at each assessment point by recall for the previous period (12 weeks prior to baseline, 12 weeks after baseline, 24 weeks after the first follow-up and 12 weeks after the second follow-up). Mean differences between groups in the EQ-5D-3L and ICECAP-A were used to measure the effectiveness of citalopram in terms of quality of life and well-being in comparison to the placebo group. The average costs for each arm were derived by multiplying the resource-use units collected in the trial by their relevant UK national-level average unit costs.[100] The unit costs used were in 2013–14 Great British pounds.

Because of the high level of missing data owing to loss of follow-up and withdrawals, extrapolation of available cost data over time up to 48 weeks was applied. In the case of individually missing cost data, mean imputation conditional on trial arm was used. The cost of patients residing in inpatient psychiatric wards was missing for three patients. For these, a conservative estimate based on the average cost of available mental health inpatient costs was imputed. For missing EQ-5D-3L and ICECAP-A information, the last available value was carried forward.

Mean outcome results over the 48 weeks were calculated based on both the available data and the imputed complete data set. Mean costs per patient over the 48 weeks were calculated using the imputed complete data set. Differences in outcomes and costs between the two groups were compared at 48 weeks based on the complete data set adjusted for respective baseline costs using regression analysis. Because no statistically significant differences between groups were found over the study period, for either costs or outcomes, incremental cost-effectiveness ratios were not calculated.[100] All analyses were carried out on an intention-to-treat basis. Calculations were made in Microsoft® Excel 2013 (Microsoft Corporation, Redmond, WA, USA) and Stata® 13.1 (StataCorp LP, College Station, TX, USA).

Chapter 3 Results

Equal numbers of participants were randomised to the two arms of the trial, minimised by centre, QLS baseline score and baseline PANSS negative subscale score. Eighty-five participants were recruited and 62 were randomised (*Figure 1*), with 46 completing assessment at the 12-week follow-up (see *Figure 1* and *Appendix 1*). This number of randomised participants fell well short of the target sample size, and therefore the power of any analysis to detect significant differences between the active and placebo groups was limited. *Table 1* provides information on the baseline demographic and clinical characteristics of the patients in the two randomised treatment arms.

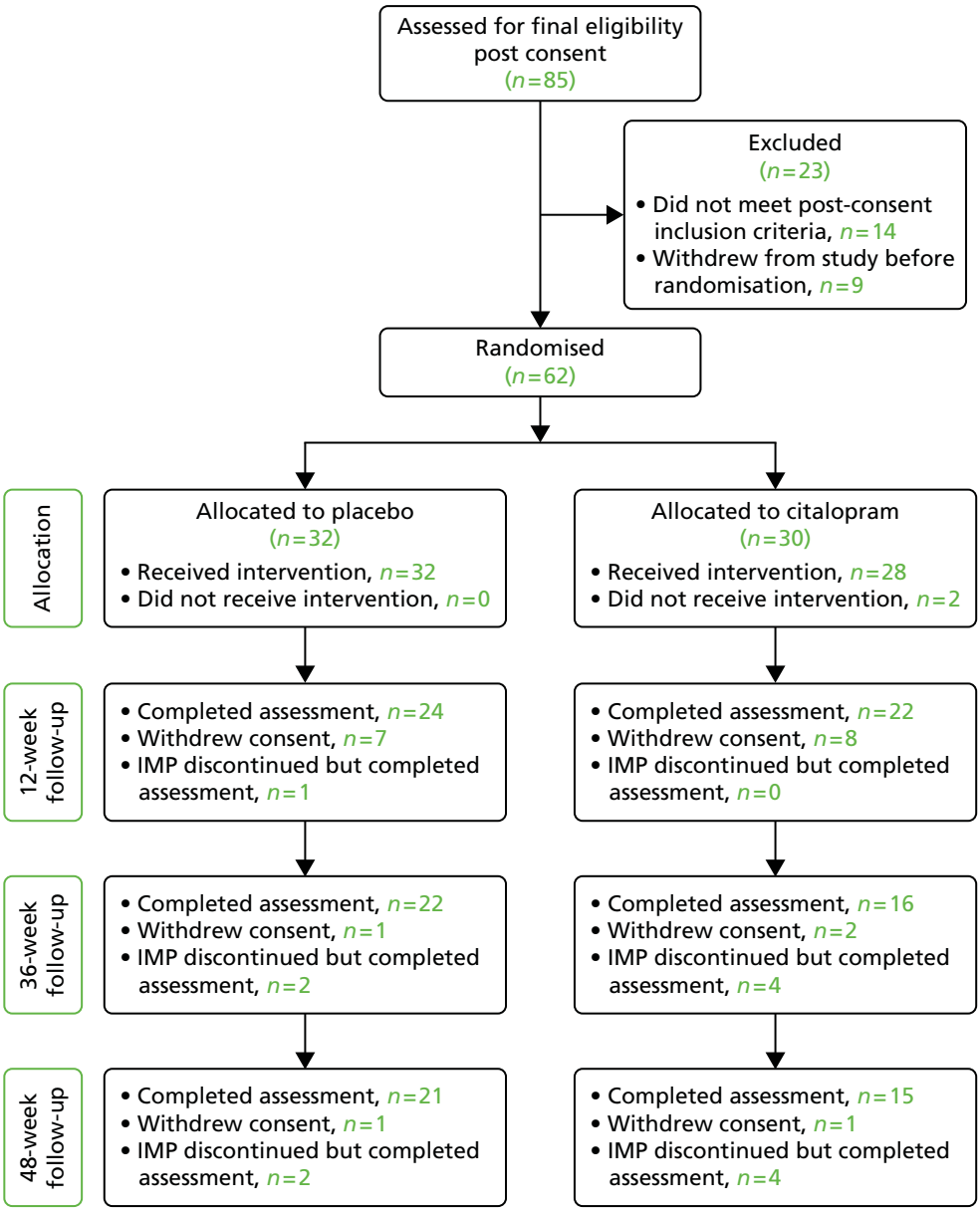

FIGURE 1 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram. IMP, investigational medicinal product.

TABLE 1 Baseline demographic and clinical characteristics of the patients in the randomised treatment arms

Variable	Placebo ($n = 32$)	Citalopram ($n = 30$)
Male (%)	22 (69)	26 (87)
Age (SD)	45.1 (12.3)	43.02 (12.3)
Mental state		
PANSS total (SD)	79.2 (16.4)	83.2 (16.4)
Depression: CDSS (SD)[a]	2.7 (3.1)	2.9 (3.5)
Quality of life		
QLS (SD)[b]	43.2 (17.3)	50.2 (17.7)
Negative symptoms		
PANSS negative subscale (SD)	25.7 (5.3)	25.3 (3.9)
PANSS negative subscale: Marder (SD)	26.0 (4.7)	25.8 (4.4)
Expressive deficits subscale (SD)	10.8 (3.3)	11.0 (2.1)
Avolition subscale (SD)	10.9 (2.2)	10.5 (2.3)
Side effects		
ANNSERS total (SD)	8.6 (8.6)	6.7 (7.7)
ANNSERS-c total (SD)	3.7 (5.3)	2.5 (3.2)
Akathisia: BARS (SD)	1.5 (3.1)	0.6 (1.5)
Parkinsonism: EPSE (SD)[c]	3.0 (4.5)	2.1 (2.8)
Tardive dyskinesia: AIMS (SD)[d]	2.7 (4.5)	2.5 (4.6)

AIMS, Abnormal Involuntary Movements Scale; BARS, Barnes Akathisia Rating Scale; EPSE, Extrapyramidal Side Effects Scale.
a Missing for $n = 1$ in placebo group and $n = 2$ in citalopram group.
b Missing for $n = 2$ in placebo group and $n = 1$ in citalopram group.
c Missing for $n = 7$ in placebo group and $n = 5$ in citalopram group.
d Missing for $n = 3$ in placebo group and $n = 5$ in citalopram group.
Data are presented as means.

Primary outcomes

The results of the data analysis presented in *Table 2* indicate that there was no difference between the two treatment arms in terms of QLS score at the primary follow-up time of 12 weeks. Those participants who were assigned to the citalopram group had slightly higher QLS scores compared with those patients who were randomised to placebo. This difference was reversed by adjustment for baseline PANSS score but the 95% CIs are wide and the difference is neither statistically nor clinically relevant. QLS scores were higher in both groups at 48 weeks post intervention. Similarly to the week-12 results, there was no difference between groups in terms of quality of life.

However, applying the criterion for a clinically significant improvement (a change of ≥ 5 points on QLS total score), a higher proportion of participants in the citalopram arm met this responder criterion (*Table 3*), although this was not deemed statistically important.

The data analysis shown in *Table 4* indicates that there was no difference between the two treatment groups in mean PANSS negative subscale score at the primary follow-up time of 12 weeks.

TABLE 2 Comparison of quality-of-life scores between the intervention (citalopram) and control (placebo) groups at 12 and 48 weeks' follow-up

	Treatment group			
	Placebo	Citalopram	Difference in QLS score (95% CI)	*p*-value
12-week follow-up	**n = *25***	**n = *21***		
QLS	49.5 (20)	52 (18.7)	2.4 (–9 to 14.0)	0.68
Adjusted QLS[a]			–5.8 (–14.3 to 2.6)	0.17
48-week follow-up	**n = *20***	**n = *17***		
QLS	54.5 (17.8)	63.1 (23)	8.7 (–6.9 to 22.3)	0.21
Adjusted QLS[a]			–0.14 (–10 to 10.1)	0.98

a Adjusted for baseline QLS.

TABLE 3 Proportion of patients in the intervention (citalopram) and control (placebo) groups meeting criterion change scores for a clinically relevant improvement on PANSS negative subscale and QLS at 12 weeks

	Treatment group		
	Placebo, *n* (%)	Citalopram, *n* (%)	Odds ratio (95% CI)
PANSS negative symptom subscale total (2-point improvement criterion)	12 (44)	15 (56)	2.1 (0.6 to 7.1)
QLS total (5-point improvement criterion)	5 (42)	7 (58)	2.0 (0.5 to 7.6)

TABLE 4 Comparison of PANSS negative subscale scores between intervention (citalopram) and control (placebo) groups at 12 weeks

	Treatment group			
	Placebo (*n* = 24)	Citalopram (*n* = 22)	Difference in PANSS negative subscale score (95% CI)	*p*-value
PANSS	23.0 (6.2)	21.5 (5.0)	–1.54 (–4.91 to 1.80)	0.36
Adjusted PANSS[a]			–1.37 (–4.12 to 1.38)	0.32

a Adjusted for baseline PANSS negative subscale score using analysis of covariance.

The participants who had been randomised to citalopram treatment had slightly higher PANSS negative subscale scores at 12 weeks than those patients who were randomised to placebo. This difference was similar after adjustment for baseline PANSS negative subscale score, indicating no difference between citalopram and placebo in terms of negative symptoms.

A clinically significant improvement in the PANSS negative subscale score is indicated by a reduction of ≥ 2 points. Patients in both groups recorded a clinically meaningful reduction in PANSS subscale score at 12-week follow-up compared with baseline, although the proportion was higher in the citalopram arm (see *Table 3*). There was no evidence that the proportion of patients who 'improved' in terms of QLS or PANSS negative symptoms differed significantly between the two groups.

Secondary outcomes

The data presented in *Tables 5* and *6* indicate that, overall, there was no difference in secondary outcomes between the intervention and control groups. There is a suggestion that lower levels of avolition (mean difference –1.3, 95% CI –2.5 to –0.09) were recorded at 12-week follow-up for participants in the citalopram group compared with the placebo group, although this difference between the treatment groups was not maintained at follow-up at 36 weeks (mean difference –0.2, 95% CI –1.7 to 1.3) or at 48 weeks (mean difference –1.3, 95% CI –3.0 to 0.4).

Similarly, there is a suggestion that lower mean ANNSERS scores were recorded for the citalopram-treated participants at 12-week follow-up, reflecting fewer and/or less-severe side effects (mean difference –4.3, 95% CI –7.9 to –0.83). Examination of this outcome at the follow-up assessment time points showed that this difference between the treatment groups was maintained at 36 weeks (mean difference –4.5, 95% CI –8.3 to –0.7) but absent at 48 weeks (mean difference –5.2, 95% CI –12.1 to 1.5).

The ANNSERS outcome was further defined as the proportion of participants who had experienced a 'severe' side effect, that is, a rating of 3 on at least one of the 34 items contributing to this score. The proportion of participants who recorded at least one 'severe' symptom was similar between groups ($n = 7$ vs. $n = 9$ in the placebo and citalopram groups, respectively).

Medication adherence

Between randomisation and 12-week follow-up, one participant in the placebo group discontinued use of study medication but agreed to continued participation in the follow-up assessments. All other participants who discontinued the study medication also completely withdrew from the trial and therefore no follow-up data were obtained. Fifteen participants allocated to citalopram and 21 allocated to placebo continued to receive trial medication for the whole 48-week follow-up period and therefore appeared to have full-trial medication adherence.

TABLE 5 Secondary outcomes recorded at the 12-week follow-up

Variable	Treatment group				Difference between groups (95% CI)[a]
	Placebo		Citalopram		
	n	Mean (SD)	*n*	Mean (SD)	
PANSS total	24	72 (16)	21	71.8 (17.8)	–1.1 (–7.7 to 5.6)
Calgary depression	24	4.7 (3.4)	21	4.3 (3.5)	–0.19 (–1.5 to 1.1)
Negative symptoms					
PANSS negative subscale (Marder)	24	22.6 (6.63)	22	22.2 (5.16)	–1.32 (–4.86 to 2.20)
Expressive deficits subscale	24	9.5 (3.7)	22	9.5 (2.9)	–0.5 (–2.0 to 1.1)
Avolition subscale	24	10.3 (2.5)	22	8.6 (2.1)	–1.3 (–2.5 to –0.09)
Side effects					
ANNSERS total	25	13.8 (10.3)	24	7.9 (6.1)	–4.3 (–7.9 to –0.83)
ANNSERS-c	25	6.7 (5.8)	24	4.7 (4.4)	–1.5 (–3.9 to 1.0)
Akathisia: BARS	25	3 (2.9)	24	0.9 (1.0)	–1.7 (–2.9 to 0.62)
Parkinsonism: EPSE	25	4.1 (4.1)	24	3.0 (2.4)	–0.7 (–2.4 to 1.0)
Tardive dyskinesia: AIMS (range)	25	3.8 (0–26)	24	1.4 (0–14)	–1.9 (–4.6 to 0.78)

AIMS, Abnormal Involuntary Movements Scale; BARS, Barnes Akathisia Rating Scale; EPSE, Extrapyramidal Side Effects Scale.
a Univariate linear regression.

TABLE 6 Secondary outcomes recorded at the 48-week follow-up

Variable	Treatment group				Difference between groups (95% CI)[a]
	Placebo		Citalopram		
	n	Mean (SD)	*n*	Mean (SD)	
PANSS total	23	6.4 (14.3)	19	61.2 (11.3)	–5.1 (–13.7 to 3.4)
Calgary depression	23	7.2 (3.2)	19	6.4 (2.8)	–0.8 (–3.1 to 1.4)
Negative symptoms					
PANSS negative	23	21.6 (6.1)	19	20.2 (5.1)	–1.4 (–5.2 to 2.3)
PANSS negative (Marder subscale)	23	21.4 (6.4)	19	19.2 (5.4)	–2.2 (–6.1 to 1.7)
Expressive deficits subscale	23	8.9 (3.7)	19	8.6 (2.4)	–0.22 (–2.3 to 1.9)
Avolition subscale	23	9.6 (2.4)	19	7.9 (2.9)	–1.3 (–3.0 to 0.4)
Side effects					
ANNSERS total	23	14.4 (12.4)	19	9.1 (8.8)	–5.2 (–12.1 to 1.5)
ANNSERS-c	23	5.0 (6.3)	19	4.8 (6.6)	–0.2 (–4.2 to 3.8)
Akathisia: BARS	23	2.3 (3.9)	19	0.84 (2.5)	–1.5 (–3.6 to 0.7)
Parkinsonism: EPSE	23	3.6 (3.8)	19	2.6 (3.6)	–1.07 (–3.4 to 1.3)
Tardive dyskinesia: AIMS (range)	23	4.1 (7.3)	19	1.2 (3.5)	–2.9 (–6.6 to 0.79)

AIMS, Abnormal Involuntary Movements Scale; BARS, Barnes Akathisia Rating Scale; EPSE, Extrapyramidal Side Effects Scale.
a Univariate linear regression.

Urgent safety measures

A main aim of this study was to identify any potential adverse effects associated with citalopram augmentation of antipsychotic medication. Plasma potassium and magnesium levels were measured at baseline while the ECG QTc interval was measured at baseline, 12, 36 and 48 weeks post study entry for all participants entering the study after the urgent safety measures were implemented. The data in *Table 7* indicate that there were no differences in mean QTc intervals between the treatment groups at any time point. This analysis was repeated, including only participants who adhered fully to the protocol and had QTc recordings at all follow-up assessments (see *Appendix 2*). There was no evidence of any difference between treatment groups in terms of length of QTc interval at any time point in this subgroup. No participant in either of the treatment groups was recorded as having a QTc that exceeded 500 milliseconds. One participant in the study (assigned to citalopram treatment) had an increase in QTc interval that was at least 60 milliseconds greater than that recorded pre randomisation.

TABLE 7 Blood chemistry and ECG QTc interval data at baseline and follow-up at 12, 36 and 48 weeks

	Treatment group				Difference between groups (95% CI)
	Placebo		Citalopram		
	n	Mean (SD)	*n*	Mean (SD)	
Plasma potassium at baseline (μg/ml)	31	4.4 (0.4)	30	4.3 (0.4)	
Plasma magnesium at baseline (μg/ml)	31	0.82 (0.07)	29	0.82 (0.07)	
QTc interval (milliseconds)					
Baseline	25	391 (26.8)	21	392 (28.7)	1.4 (–1.3 to 4.5)
12 weeks	21	384 (29.0)	14	381(40.1)	2.4 (–8.3 to 5.6)
36 weeks	20	384 (29.7)	13	384 (40)	–1.6 (–4.0 to 2.2)
48 weeks	19	383 (30.3)	12	380.3 (39)	6.3 (–16.4 to 28.9)

Health economics analysis

The final economic analysis was based on the 30 study participants randomised to citalopram and the 32 participants randomised to placebo. *Appendix 3* shows the number of patients with available health economics data by information category at each assessment point.

Table 8 summarises the baseline characteristics of the participants relevant for the economic analysis. Participants in the citalopram arm had a somewhat lower duration of illness compared with the placebo arm (14 years vs. 18 years, respectively). Considerably more patients in the placebo arm also lived in an inpatient mental health facility at baseline (15.63% vs. 3.33%, respectively). Only five patients had any kind of employment at any point in time over the trial period.

TABLE 8 Baseline demographic and clinical characteristics of the participants, relevant for the economic analysis

Variable	Placebo	Citalopram
Duration of illness (years), *n* [mean (SD)]	30 [18.10 (11.83)]	26 [13.96 (10.05)]
Employment, *n* (%)		
At least part time (at any point in study)	2 (6.25)	3 (10)
Accommodation, *n* (%)		
Independently or with family	17 (53.13)	24 (80)
Inpatient mental health facility	5 (15.63)	1 (3.33)
Nursing home	1 (3.13)	0
Sheltered/supported accommodation	6 (18.75)	4 (13.33)
Missing	3 (9.38)	1 (3.33)
Primary clinical diagnosis (ICD-10), *n* (%)		
Schizophrenia	28 (87.5)	27 (90)
Schizoaffective disorder	2 (6.25)	1 (3.33)
Schizophreniform disorder	0	1 (3.33)
Other psychotic disorders (including bipolar)	1 (3.13)	0
Missing	1 (3.13)	1 (3.33)
Ethnicity, *n* (%)		
White	23 (71.88)	23 (76.67)
Black	4 (12.5)	4 (13.33)
Asian	5 (15.62)	3 (10)
Missing	0	0
Costs, *n* [mean (SD)]		
Mental health outpatient	32 [658.23 (1415.60)]	30 [363.36 (354.27)]
Mental health inpatient[a]	32 [2241.80 (5965.49)]	30 [342.34 (1811.51)]
Non-mental health outpatient	32 [261.71 (731.23)]	30 [35.78 (105.89)]
Non-mental health inpatient[a]	32 [451.23 (2471.48)]	30 [0 (0)]
Primary care	32 [85.52 (125.26)]	30 [49.55 (65.01)]
Medications	32 [216.50 (168.12)]	30 [275.34 (272.96)]
Social care	32 [210.19 (542.07)]	30 [165.91 (463.98)]
Absenteeism[a]	32 [226.06 (1238.21)]	30 [8.06 (42.62)]
Informal care	32 [228.47 (512.72)]	30 [309.31 (657.85)]

ICD-10, *International Classification of Diseases*, Tenth Revision.

a Cost categories with considerable imbalance at baseline. These seemingly large differences in baseline costs between the placebo and treatment arms are because of the small number of patients with values other than zero and the unequal distribution of these few patients between the two arms (mental health inpatient costs > 0: $n = 7$ in the placebo arm and $n = 1$ in the citalopram arm; non-mental health inpatient costs > 0: $n = 1$ in the placebo arm and $n = 0$ in the citalopram arm; absenteeism costs > 0: $n = 1$ in the placebo arm and $n = 1$ in the citalopram arm).

Baseline costs are important for recognising potential differences between the two arms in health-care utilisation prior to randomisation. At baseline, costs tended to be higher in the placebo arm but differences compared with the treatment arm were not statistically significant (for all $p > 0.05$). However, the mental health and non-mental health inpatient costs and the cost of absenteeism in the two arms were considerably imbalanced at baseline (see *Table 8*).

Appendix 4 lists the types of the health-care, social care and voluntary sector services used by any of the patients in the ACTIONS study and their respective UK national-level unit costs with source information. The participants with the highest costs at baseline (and throughout the study) were those who were living in an inpatient mental health setting and those who used additional drug and/or alcohol addiction services.

There was a slight trend towards improvement in quality of life and well-being measured by the EQ-5D-3L and the ICECAP-A, respectively, in both arms as shown in *Tables 9* and *10*. This trend was observable both in the available case and imputed complete data sets. There was no evidence of a significant difference in terms of improvement between the citalopram and the placebo arms in neither the EQ-5D-3L ($p = 0.250$) nor ICECAP-A ($p = 0.248$).

TABLE 9 Mean EQ-5D-3L per patient over the 48-week follow-up

	Baseline	12 weeks	36 weeks	48 weeks
Available case data, *n* [mean (SD)]				
Full cohort	60 [0.73 (0.20)]	47 [0.80 (0.18)]	44 [0.72 (0.27)]	40 [0.79 (0.22)]
Placebo	31 [0.69 (0.21)]	25 [0.78 (0.16)]	24 [0.68 (0.42)]	23 [0.78 (0.40)]
Treatment	29 [0.76 (0.24)]	22 [0.82 (0.3)]	20 [0.77 (0.39)]	17 [0.81 (0.44)]
Imputed complete data set, *n* [mean (SD)]				
Full cohort	62 [0.73 (0.20)]	62 [0.80 (0.16)]	62 [0.75 (0.19)]	62 [0.78 (0.20)]
Placebo	32 [0.69 (0.20)]	32 [0.78 (0.14)]	32 [0.74 (0.19)]	32 [0.78 (0.17)]
Treatment	30 [0.76 (0.19)]	30 [0.82 (0.17)]	30 [0.75 (0.18)]	30 [0.78 (0.23)]

TABLE 10 Mean ICECAP-A per patient over the 48-week follow-up

	Baseline	12 weeks	36 weeks	48 weeks
Available case data, *n* [mean (SD)]				
Full cohort	59 [0.64 (0.20)]	47 [0.69 (0.22)]	44 [0.67 (0.18)]	40 [0.72 (0.18)]
Placebo	31 [0.64 (0.24)]	24 [0.64 (0.35)]	24 [0.67 (0.33)]	23 [0.73 (0.36)]
Treatment	28 [0.65 (0.24)]	23 [0.73 (0.36)]	20 [0.67 (0.36)]	17[0.71 (0.39)]
Imputed complete data set, *n* [mean (SD)]				
Full cohort	62 [0.64 (0.19)]	62 [0.69 (0.20)]	62 [0.68 (0.16)]	62 [0.71 (0.17)]
Placebo	32 [0.64 (0.21)]	32 [0.64 (0.20)]	32 [0.67 (0.15)]	32 [0.73 (0.13)]
Treatment	30 [0.65 (0.18)]	30 [0.73 (0.18)]	30 [0.68 (0.18)]	30 [0.68 (0.20)]

After adjusting for baseline differences, there was no statistically significant difference between the arms in any of the cost categories, except non-mental health inpatient costs. This borderline significant difference in non-mental health inpatient costs ($p = 0.05$) is, however, a result of having only two patients in the available sample (both in the citalopram arm) with positive resource use in this category, and cannot be seen as evidence of difference because of the small overall sample size (*Table 11*).

TABLE 11 Mean costs per patient over the 48-week follow-up period (in £ for year 2013/14)

Imputed full data set	Placebo ($n = 32$), mean (SD)	Citalopram ($n = 30$), mean (SD)	Placebo vs. citalopram	
			p-value[a]	Mean difference (95% CI)
Total medication costs (£)				
Oral and depot medication	791.52 (612.94)	980.82 (850.78)	0.822	–189.30 (–564.21 to 185.62)
Total other health and social care costs (£)				
Mental health outpatient	1706.19 (2420.68)	1876.12 (1882.55)	0.140	–169.94 (–1276.72 to 936.85)
Mental health inpatient	1864.31 (5486.411)	132.57 (726.13)	0.621	1731.74 (–289.32 to 3752.79)
Non-mental health outpatient	132.18 (226.89)	196.61 (280.84)	0.370	–64.44 (–193.76 to 64.88)
Non-mental health inpatient	0 (0)	48.27 (134.04)	0.050	–48.27 (–95.64 to –0.90)
Primary care	156.58 (162.10)	128.46 (112.58)	0.750	28.12 (–43.23 to 99.478)
Social care	376.61 (693.82)	278.01 (525.61)	0.562	98.59 (–215.69 to 412.89)
Total health and social care costs (£)	5027.38 (6034.78)	3640.86 (2226.41)	0.516	1386.52 (–954.76 to 3727.80)
Indirect costs (£)				
Absenteeism	848.65 (3699.76)	38.98 (148.37)	0.245	809.65 (–543.24 to 2162.53)
Informal care	7399.28 (11940.38)	7484.49 (14152.12)	0.893	–85.21 (–6722.24 to 6551.81)
Total indirect costs (£)	8247.90 (12778.27)	7523.47 (14209.25)	0.892	724.43 (–6132.50 to 7581.38)
Total societal costs (£)	13275.28 (13941.2)	11164.33 (15028.73)	0.972	2110.95 (–5248.32 to 9470.22)

a *p*-values adjusted for baseline differences.

Chapter 4 Discussion

The ACTIONS trial includes the largest sample of patients assigned to citalopram in a published, double-blind RCT of antipsychotic augmentation targeted at the negative symptoms of schizophrenia, and has the longest follow-up period. Nevertheless, the trial under-recruited and therefore the power of any analysis to detect significant differences between the active and placebo groups was limited. Comparison of the citalopram and placebo arms failed to show any superior therapeutic benefit for adjunctive citalopram over placebo over 12 weeks and at 1 year, in terms of improvement in mean scores for quality of life or decreased negative symptoms of schizophrenia. This finding is in line with the results of two, relatively recent, double-blind RCTs of adjunctive citalopram for the treatment of negative symptoms in schizophrenia, one lasting 4 weeks[101] and the other 6 months.[102] Both trials failed to find any statistically significant difference between citalopram- and placebo-treated groups on the PANSS negative symptom subscale. However, in ACTIONS it may be noted that when a priori criteria for a clinically relevant improvement were applied, a higher proportion of participants in the citalopram group fulfilled the criterion for a clinically relevant improvement on the QLS score at 12 weeks than in the placebo group. Furthermore, in the citalopram group nearly 60% of participants at 12 weeks fulfilled the criterion for a clinically relevant improvement on the PANSS negative symptom subscale compared with just over 40% of those assigned to placebo. There was no difference between the two treatment groups in the frequency or severity of adverse effects.

Primary outcomes: quality of life and negative symptoms

No differences emerged between the two treatment groups on the quality-of-life measure. In relation to negative symptoms, there were no differences between the treatment groups on overall negative symptoms scores but there was a suggestion that, after 12 weeks of treatment, those participants treated with citalopram had lower levels of avolition/amotivation. A differential improvement of separate negative symptom domains in response to antidepressant medication has been reported before.[103] Had ACTIONS recruited to target, the intention was to include depression scores as a covariate to determine whether or not any difference between groups at follow-up in negative symptoms could be explained by amelioration of depressive features in the citalopram group. The limited power of the study does not allow us to do this for the avolition finding using the originally planned methodology. However, the treatment groups did not differ significantly on depression scores at follow-up, so there is no indication that differences found in avolition can be explained by the antidepressant effect of citalopram. This finding of a possible preferential effect of citalopram on the avolition/amotivation negative symptom domain has, perhaps, two possible implications. First, it suggests that citalopram may be worthy of further investigation as an adjunctive medication in patients with established schizophrenia and negative symptoms. A key rationale for such treatment in clinical practice is to render a patient more disposed to, and more able to engage with, psychosocial interventions and thus increase the effectiveness of rehabilitation programmes. Avolition/amotivation is recognised as a critical barrier to such psychosocial rehabilitation and to achieving better functional outcomes,[104–107] and is a therefore a critical treatment target in this context. Second, this finding supports the view that future studies examining the treatment response of negative symptoms in schizophrenia should use rating scales that allow for a valid and separate evaluation of avolition/amotivation.[106,107]

Secondary outcomes: safety and tolerability of citalopram

Detailed and comprehensive assessment of medication side effects throughout the follow-up period did not yield any evidence for a greater side-effect burden with adjunctive citalopram compared with placebo. Indeed, the findings suggest a slightly lower general side-effect burden for the citalopram-treated participants at 12 and 36 weeks' follow-up. This suggests that citalopram is generally well tolerated in people with schizophrenia on antipsychotic medication, but it is also a plausible speculation that the lower side-effect score in the citalopram-treated group may partly reflect some alleviation of anxiety symptoms that participants had attributed to their medication[108] and thus reported as side effects.

There was no difference between the treatment groups in terms of duration of QTc interval at any time point. No participant had a QTc duration of more than 500 milliseconds and only one had an increase in the QTc of more than 60 milliseconds, thresholds that are generally taken as an indication to stop medication because of the risk of potentially fatal cardiac arrhythmias such as Torsades de pointes.[109,110] Thus, there was little in the limited QTc interval data collected in this study to suggest that citalopram has any increased risk for QTc interval prolongation in individuals prescribed concomitant antipsychotic medication.

Health economics analysis

It appears from the health economics analysis that there is no statistically significant difference between the two arms over the 48-week follow-up period in either the health economics outcomes or costs. Given the small sample size and large instance of losses to follow-up and withdrawals, the data were not adequately powered to discern any small difference between the two groups that might exist. Nevertheless, citalopram is a relatively low-cost intervention, with a mean medication cost of £27.62 per patient in the treatment arm. Safety concerns and the additional clinical tests required, however, may make the use of this medication considerably more expensive and less suitable for the target population. This study highlights the importance of balancing mental health trial arms at baseline according to usual accommodation, collecting baseline cost information and correcting for any imbalance in the respective cost categories in the health economic analysis.

One of the major limitations of this economic analysis is the small sample size. Particular costs could be under-represented; for example, the cost of living in sheltered/supported accommodation, nursing homes and inpatient mental health facilities. The considerable differences in mental health inpatient and non-mental health inpatient costs, favouring the citalopram arm in the first instance, are the result of the small number of cases with actual resource use in these cost categories (citalopram arm $n = 1$, placebo arm $n = 14$; citalopram arm $n = 0$, placebo arm $n = 10$; for mental health inpatient and non-mental health inpatient costs, respectively) and the existing baseline imbalance between the trial arms. We could account for baseline differences, but not for the small case numbers, using regression analysis.

Resource-use data collection was based on patient recall, checked where possible against patient records by the investigators. Owing to the large number of patients lost to follow-up and withdrawals, and some other study hurdles, the current data on resource use are prone to error, likely causing an underestimation of real-life costs for this patient cohort; thus, the current cost estimates should be used with caution.

Some further limitations of the analysis include the lack of carer perspective. Although investigating this was also one of the original intentions of the trial, because of difficulties in recruiting and following up patients in addition to identifying primary informal carers, these data could not be collected. Such data could be particularly useful in identifying further benefits or detriments of the treatment.

Recruitment

From the beginning of this trial, we encountered various barriers to recruiting participants to time and target, as appears to be the case for many trials in the UK and particularly so for those conducted in mental health services.[111] Negotiation of the hurdles of research governance, regulation and NHS permissions, contracts and costs allocation meant that opening the study sites was a slower process than expected, resulting in the waste of many valuable months for recruitment. Once sites were open to recruitment, referrals to the study were patchy and often ebbed to non-existent, despite feasibility work prior to this trial indicating that a large proportion of patients would be eligible. These were not refusals on the part of eligible patients but rather that patients were not being given an opportunity to take part. Referrals must come from a member of the patient's clinical team, and clinical teams could have competing clinical priorities, concerns about how introducing a trial to the patient might impact on their therapeutic relationship, a lack understanding of the clinical equipoise of the research question, and/or safety concerns (see *Urgent safety measures*). The result was that recruitment occurred in focused areas where sympathetic clinical staff were found, and many eligible patients in other areas missed the opportunity to participate. Additional trial sites were opened over time in order to access more eligible patients and the trial was promoted using talks to clinical teams, newsletters and researcher recruitment training days that covered engagement of both patients and clinical staff. Adopting more pragmatic eligibility criteria was also considered, but was not implemented as the majority of these criteria reflected safety requirements, compromise on the clearly defined target population was unwanted, and the screening log information did not identify any particular criterion whose modification would have led to a substantial increase in participant numbers.

Urgent safety measures

New safety information about citalopram was published by the manufacturer in conjunction with the MHRA in late 2011,[99] with a warning about the risk of QTc prolongation and stating that coadministration of citalopram with medicines that prolong the QT interval (including antipsychotic drugs) was therefore contraindicated. This warning by the MHRA and a similar warning from the US Food and Drug Administration (FDA) that citalopram should no longer be used at doses greater than 40 mg per day were prompted by the results of a small study of the effects of citalopram on the QT interval. Howland[92] considered that 'The statistically significant results from this "thorough QT/QTc study" were small in magnitude, and their clinical significance is questionable'. He concluded that 'Based on the studies reviewed . . . the citalopram dose limitations described in the FDA safety announcement do not have strong clinical justification'.[93] The validity of the warnings was also challenged in a subsequent review of the relevant literature by Vieweg *et al.*,[112] who concluded that, in contrast to statements made by the manufacturer of citalopram and the FDA in August 2011, they had not been able to find 'convincing evidence that citalopram, when used as prescribed in doses above 40 mg/day, was associated with an increased risk of QTc interval prolongation and Torsade de pointes, as long as clinicians attended to well-known risk factors'.

Consequent on the MHRA warning, urgent safety measures, agreed with the MHRA, were implemented immediately. However, conflicting decisions by the MHRA and the REC impacted adversely on the progress of the trial. A tardy response from the REC regarding the substantial amendment related to the implementation of the urgent safety measures gave an unfavourable opinion and, unlike the MHRA, considered that the QT interval should be checked prior to initiating trial medication and that the trial should revert to using the approved documents that pre-dated the changes deemed necessary by the MHRA. Following advice from the study sponsor and the MHRA Clinical Trials Unit, no further participants were randomised into the trial but the trial medication was not discontinued for any participant already enrolled. Eventually, the National Research Ethics Service agreed that it would be acceptable for the research to proceed under the urgent safety measures previously implemented and later REC approval was given with the addition of QTc monitoring. However, there was a negative impact on recruitment, with one study site withdrawing support, expressing the view the trial would now have less bearing on clinical practice, and persistent reluctance from clinicians to support the study as the trial medication regimen was not compatible with the implementation of the MHRA warning in their clinical service.

Conclusions

This trial under-recruited, falling well short of the target of 358 participants, which reflects the range of barriers to recruitment that were encountered; in particular, the impact of a MHRA warning about cardiac problems with citalopram which was issued shortly after the study commenced recruitment. This warning contraindicated the combination of citalopram and an antipsychotic agent, and required the implementation of urgent safety measures in the trial. Given the relatively small sample size achieved, the power of any statistical analysis to detect clinical or statistically meaningful significant differences between the citalopram and placebo groups was limited.

The trial found no difference between treatment groups on the primary outcome measures over a follow-up period of up to 1 year. The question of whether or not statistically significant differences would have been identified with the original sample size is moot, as is whether or not further trials of such an augmentation strategy for persistent negative symptoms in people with established schizophrenia are warranted. However, the secondary analysis of the data in this relatively small trial suggested a modest, positive effect on the negative symptom subdomain, avolition/amotivation, which is recognised as a critical barrier to psychosocial rehabilitation and to achieving better social and community functional outcomes. If there are future studies of this treatment strategy, rating scales that allow for evaluation of avolition/amotivation as a distinct and separate negative symptom domain should be used.

With regard to health economic measures, there were no statistically significant differences between the citalopram and placebo arms but a considerably larger sample size may be needed to draw robust conclusions on the cost-effectiveness of the use of antidepressants in combination with antipsychotics to treat persistent negative symptoms in people with schizophrenia who do not fulfil the criteria for major depression. Our study highlights the importance of balancing the treatment arms at baseline in such trials according to usual accommodation, collecting baseline cost information and correcting for any imbalance in a respective health economic analysis.

Regarding choice of antidepressant, information on the relative merits of available antidepressants in this treatment context is limited, so the rationale for originally choosing citalopram for this study largely reflected its relatively favourable safety and tolerability profile. The publication of some limited data on QTc prolongation with citalopram resulted in the MHRA safety warning and brought our choice of antidepressant into question. However, the contraindication of the prescription of the combination of citalopram and an antipsychotic drug was based on evidence that antipsychotic medication also has the potential for QTc prolongation, rather than any data clarifying the impact on QTc interval of this particular combination. Overall, comprehensive assessment of side-effect burden in this trial did not identify any serious safety or tolerability issues for citalopram as an adjunct to continuing antipsychotic medication; citalopram did not increase the side-effect burden or have any evident effect on QTc. However, if adjunctive citalopram were to be tested in future trials, appropriate cardiac monitoring should be in place to further assess the safety of this drug combination.

The viability of adjunctive antidepressant treatment as a long-term prescribing strategy for the treatment of negative symptoms in schizophrenia may merit further investigation but the ability to recruit an adequate sample size remains a barrier to any trial conducted in a similar clinical setting. Leaving aside the exceptional issue of the necessary urgent safety measures, the various strategies we adopted to overcome the barriers to recruitment identified did not allow the target sample size to be achieved, and so we are unable to derive any recommendations for ensuring an adequate recruitment rate in future similar trials.

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Contributions of authors

Thomas RE Barnes (Professor of Clinical Psychiatry) was the principal grant applicant, developed the trial protocol and was responsible for the overall conduct of the trial as chief investigator. He led the interpretation of the results and drafting of the final report.

Verity C Leeson (Clinical Trials Manager) contributed to the development of the original trial protocol and its amendments, and was responsible for the day-to-day management of the trial. She contributed to the interpretation of the results and preparation of the final report.

Carol Paton (Chief Pharmacist) cowrote the original grant application, was a principal investigator, contributed to the trial protocol and its amendments, and to the interpretation of the results for the final report.

Céire Costelloe (Career Development Fellow) led the statistical analysis and contributed to the interpretation and write-up of the results for the final report.

Judit Simon (Professor of Health Economics) contributed to the original grant application and the development of the trial protocol. She co-led the health economics analysis and write-up.

Noemi Kiss (Health Economics Researcher) co-led the health economics analysis and write-up.

David Osborn (Professor of Psychiatric Epidemiology) cowrote the original grant application, was a principal investigator and commented on earlier drafts of the final report.

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Data sharing statement

All data are available on request from the corresponding author.

References

1. Kraepelin E. *Dementia Praecox and Paraphrenia*. New York, NY: RE Krieger; 1919.
2. Bleuler E. *Dementia Praecox or the Group of Schizophrenias*. New York, NY: International Universities Press; 1950.
3. Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC. Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. *Am J Psychiatry* 1998;**155**:1196–201. http://dx.doi.org/10.1176/ajp.155.9.1196
4. Milev P, Ho BC, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry* 2005;**162**:495–506. http://dx.doi.org/10.1176/appi.ajp.162.3.495
5. Blanchard JJ, Horan WP, Collins LM. Examining the latent structure of negative symptoms: is there a distinct subtype of negative symptom schizophrenia? *Schizophr Res* 2005;**77**:151–65. http://dx.doi.org/10.1016/j.schres.2005.03.022
6. Hofer A, Baumgartner S, Edlinger M, Hummer M, Kemmler G, Rettenbacher MA, *et al.* Patient outcomes in schizophrenia I: correlates with sociodemographic variables, psychopathology, and side effects. *Eur Psychiatry* 2005;**20**:386–94. http://dx.doi.org/10.1016/j.eurpsy.2005.02.005
7. Rosenheck R, Leslie D, Keefe R. Barriers to employment for people with schizophrenia. *Am J Psychiatry* 2006;**163**:411–17. http://dx.doi.org/10.1176/appi.ajp.163.3.411
8. Kurtz MM, Moberg PJ, Ragland JD, Gur RC, Gur RE. Symptoms versus neurocognitive test performance as predictors of psychosocial status in schizophrenia: a 1- and 4-year prospective study. *Schizophr Bull* 2005;**31**:167–74. http://dx.doi.org/10.1093/schbul/sbi004
9. Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry* 2006;**163**:418–25. http://dx.doi.org/10.1176/appi.ajp.163.3.418
10. Green MF, Nuechterlein KH. Should schizophrenia be treated as a neurocognitive disorder? *Schizophr Bull* 1999;**25**:309–18. http://dx.doi.org/10.1093/oxfordjournals.schbul.a033380
11. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? *Schizophr Bull* 2006;**32**:250–8. http://dx.doi.org/10.1093/schbul/sbj011
12. Selten JP, Wiersma D, van den Bosch RJ. Distress attributed to negative symptoms in schizophrenia. *Schizophr Bull* 2000;**26**:737–44. http://dx.doi.org/10.1093/oxfordjournals.schbul.a033490
13. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull* 2006;**32**:214–19. http://dx.doi.org/10.1093/schbul/sbj053
14. Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. *Schizophr Bull* 2007;**33**:1013–22. http://dx.doi.org/10.1093/schbul/sbl057
15. Messinger JW, Trémeau F, Antonius D, Mendelsohn E, Prudent V, Stanford AD, *et al.* Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. *Clin Psychol Rev* 2011;**31**:161–8. http://dx.doi.org/10.1016/j.cpr.2010.09.002
16. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. *Biol Psychiatry* 2010;**67**:902–11. http://dx.doi.org/10.1016/j.biopsych.2009.10.020

17. Strauss GP. The emotion paradox of anhedonia in schizophrenia: or is it? *Schizophr Bull* 2013;**39**:247–50. http://dx.doi.org/10.1093/schbul/sbs192

18. King DJ. Atypical antipsychotics and the negative symptoms of schizophrenia. *Adv Psychiatr Treat* 1998;**4**:53–61. http://dx.doi.org/10.1192/apt.4.1.53

19. Erhart SM, Marder SR, Carpenter WT. Treatment of schizophrenia negative symptoms: future prospects. *Schizophr Bull* 2006;**32**:234–7. http://dx.doi.org/10.1093/schbul/sbj055

20. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;**353**:1209–23. http://dx.doi.org/10.1056/NEJMoa051688

21. Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, Hayhurst KP, *et al.* Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CutLASS 1). *Arch Gen Psychiatry* 2006;**63**:1079–87. http://dx.doi.org/10.1001/archpsyc.63.10.1079

22. Buchanan R, Breier A, Kirkpatrick B, Ball P, Carpenter WT Jr. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *Am J Psychiatry* 1998;**155**:751–60.

23. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *Am J Psychiatry* 1999;**156**:990–9.

24. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;**373**:31–41. http://dx.doi.org/10.1016/S0140-6736(08)61764-X

25. Barnes TRE, Paton C. Uncertainties page: do antidepressants improve negative symptoms in schizophrenia? *BMJ* 2011;**342**:d3371. http://dx.doi.org/10.1136/bmj.d3371

26. Caforio G, Di Giorgio A, Rampino A, Rizzo M, Romano R, Taurisano P, *et al.* Mirtazapine add-on improves olanzapine effect on negative symptoms of schizophrenia. *J Clin Psychopharmacol* 2013;**33**:810–12. http://dx.doi.org/10.1097/JCP.0b013e3182a4ec77

27. Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. *J Clin Psychopharmacol* 2012;**32**:179–85. http://dx.doi.org/10.1097/JCP.0b013e318248b7bb

28. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization; 1992.

29. Prescribing Observatory for Mental Health. *Topic 6. Assessment of the Side Effects of Depot Antipsychotics: Baseline Audit Report 2008*. London: Royal College of Psychiatrists; 2008.

30. Prescribing Observatory for Mental Health. *Topic 3 Report 3a. Prescribing of High Dose and Combined Antipsychotics for Patients on Forensic Wards: Baseline Audit*. London: Royal College of Psychiatrists; 2007.

31. Buchanan RW, Brandes M, Breier A. Treating Negative Symptoms: Pharmacological Strategies. In Breier A, editor. *The New Pharmacotherapy of Schizophrenia*. Washington, DC: American Psychiatric Press; 1996. pp. 179–204.

32. Goff DC, Evins AE. Negative symptoms in schizophrenia: neurobiological models and treatment response. *Harv Rev Psychiatry* 1998;**6**:59–77. http://dx.doi.org/10.3109/10673229809000313

33. Siris SG, Mason SE, Bermanzohn PC, Alvir JM, McCorry TA. Adjunctive imipramine maintenance in post-psychotic depression/negative symptoms. *Psychopharmacol Bull* 1990;**26**:91–4.

34. Evins AE. Adjunctive antidepressant drug therapies in the treatment of negative symptoms of schizophrenia. *CNS Drugs* 1996;**6**:130–47. http://dx.doi.org/10.2165/00023210-199606020-00005

35. Möller HJ. Non-neuroleptic approaches to treating negative symptoms in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2004;**254**:108–16. http://dx.doi.org/10.1007/s00406-004-0503-4

36. Silver H, Nassar A. Fluvoxamine improves negative symptoms in treated chronic schizophrenia: an add-on double-blind, placebo-controlled study. *Biol Psychiatry* 1992;**31**:698–704. http://dx.doi.org/10.1016/0006-3223(92)90279-9

37. Spina E, De Domenico P, Ruello C, Longobardo N, Gitto C, Ancione M, *et al.* Adjunctive fluoxetine in the treatment of negative symptoms in chronic schizophrenic patients. *Int Clin Psychopharmacol* 1994;**9**:281–5. http://dx.doi.org/10.1097/00004850-199400940-00007

38. Goff DC, Midha KK, Sarid-Segal O, Hubbard JW, Amico E. A placebo-controlled trial of fluoxetine added to neuroleptic in patients with schizophrenia. *Psychopharmacology* 1995;**117**:417–23. http://dx.doi.org/10.1007/BF02246213

39. Salokangas RK, Saarijärvi S, Taiminen T, Kallioniemi H, Lehto H, Niemi H, *et al.* Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. *Acta Psychiatr Scand* 1996;**94**:175–80. http://dx.doi.org/10.1111/j.1600-0447.1996.tb09844.x

40. Taiminen TJ, Syvälahti E, Saarijärvi S, Lehto H, Niemi H, Ahola V, *et al.* Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. *Int Clin Psychopharmacol* 1997;**12**:31–5. http://dx.doi.org/10.1097/00004850-199701000-00004

41. Jockers-Scherübl MC, Bauer A, Godemann F, Reischies FM, Selig F, Schlattmann P. Negative symptoms of schizophrenia are improved by the addition of paroxetine to neuroleptics. *Int Clin Psychopharmacol* 2005;**20**:27–31. http://dx.doi.org/10.1097/00004850-200501000-00006

42. Saito M, Yasui-Furukori N, Nakagami T, Furukori H, Kaneko S. Dose-dependent interaction of paroxetine with risperidone in schizophrenic patients. *J Clin Psychopharmacol* 2005;**25**:527–32. http://dx.doi.org/10.1097/01.jcp.0000185428.02430.c7

43. Buchanan RW, Kirkpatrick B, Bryant N, Ball P, Breier A. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. *Am J Psychiatry* 1996;**153**:1625–7. http://dx.doi.org/10.1176/ajp.153.12.1625

44. Zocalli R, Muscatello MR, Cedro C, Neri P, La Torre D, Spina E, *et al.* The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia. *Int Clin Psychopharmacol* 2004;**19**:71–6. http://dx.doi.org/10.1097/00004850-200403000-00003

45. Zoccali R, Muscatello MR, Torre DL, Malara G, Canale A, Crucitti D, *et al.* Lack of a pharmacokinetic interaction between mirtazapine and the newer antipsychotics clozapine, risperidone and olanzapine in patients with chronic schizophrenia. *Pharmacol Res* 2003;**48**:411–14. http://dx.doi.org/10.1016/S1043-6618(03)00178-6

46. Berk M, Ichim C. Brook S. Efficacy of mirtazapine add on therapy to haloperidol in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Int Clin Psychopharmacol* 2001;**16**:87–92. http://dx.doi.org/10.1097/00004850-200103000-00003

47. Vidal C, Reese C, Fisher BA, Chiapelli J, Himelhocj S. Meta-analysis of efficacy of mirtazapine as an adjunctive treatment of negative symptoms in schizophrenia. *Clin Schizophr Related Psychoses* 2015:**9**:88–95. http://dx.doi.org/10.3371/CSRP.VIRE.030813

48. Shoja-Shafti S. Treatment-responsiveness of negative symptoms in schizophrenia: a double-blind placebo-control clinical trial. *Iran J Med Sci* 2006;**31**:135–8.

49. Silver H, Shmugliakov N. Augmentation with fluvoxamine but not maprotiline improves negative symptoms in treated schizophrenia: evidence for a specific serotonergic effect from a double-blind study. *J Clin Psychopharmacol* 1998;**18**:208–11. http://dx.doi.org/10.1097/00004714-199806000-00005

50. Chertkow Y, Weinreb O, Youdim MBH, Silver H. Dopamine and serotonin metabolism in response to chronic administration of fluvoxamine and haloperidol combined treatment. *J Neural Transm* 2007;**114**:1443–54. http://dx.doi.org/10.1007/s00702-007-0753-1

51. Zullino D, Delacrausaz P, Baumann P. [The place of SSRIs in the treatment of schizophrenia.] *L'Encéphale* 2002;**28**:433–8.

52. Jones CA, McCreary AC. Serotonergic approaches in the development of novel antipsychotics. *Neuropharmacology* 2008;**55**:1056–65. http://dx.doi.org/10.1016/j.neuropharm.2008.05.025

53. Rummel C, Kissling W, Leucht S. Antidepressants as add-on treatment to antipsychotics for people with schizophrenia and pronounced negative symptoms: a systematic review of randomized trials. *Schizophr Res* 2005;**80**:85–97. http://dx.doi.org/10.1016/j.schres.2005.07.035

54. Sepehry AA, Potvin S, Elie R, Stip E. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. *J Clin Psychiatry* 2007;**68**:604–10. http://dx.doi.org/10.4088/JCP.v68n0417

55. Lecrubier Y, Perry R, Milligan G, Leeuwenkamp O, Morlock R. Physician observations and perceptions of positive and negative symptoms of schizophrenia: a multinational, cross-sectional survey. *Eur Psychiatry* 2007;**22**:371–9. http://dx.doi.org/10.1016/j.eurpsy.2007.03.003

56. Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry* 2010;**197**:174–9. http://dx.doi.org/10.1192/bjp.bp.109.067710

57. Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, *et al.* Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull* 2015;**41**:892–9. http://dx.doi.org/10.1093/schbul/sbu170

58. Rummel C, Kissling W, Leucht S. Antidepressants for the negative symptoms of schizophrenia. *Cochrane Database Syst Rev* 2006;**3**:CD005581.

59. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association; 2000.

60. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, *et al.* Practice guideline for the treatment of patients with schizophrenia. Second edition. *Am J Psychiatry* 2004;**161**(Suppl. 2):1–56.

61. Kramer MS, Vogel WH, DiJohnson C, Dewey DA, Sheves P, Cavicchia S, *et al.* Antidepressants in 'depressed' schizophrenic inpatients: a controlled trial. *Arch Gen Psychiatry* 1989;**46**:922–8. http://dx.doi.org/10.1001/archpsyc.1989.01810100064012

62. Plasky P. Antidepressant usage in schizophrenia. *Schizophr Bull* 1991;**17**:649–57. http://dx.doi.org/10.1093/schbul/17.4.649

63. Siris S. Diagnosis of secondary depression in schizophrenia: implications for DSM-IV. *Schizophr Bull* 1991;**17**:75–98. http://dx.doi.org/10.1093/schbul/17.1.75

64. Glick ID, Pham D, Davis JM. Concomitant medications may not improve outcome of antipsychotic monotherapy for stabilized patients with non-acute schizophrenia. *J Clin Psychiatry* 2006;**67**:1261–5. http://dx.doi.org/10.4088/JCP.v67n0813

65. Tandon R, Targum SD, Nasrallah HA. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. *J Psychiatr Prac* 2006;**12**:348–63. http://dx.doi.org/10.1097/00131746-200611000-00003

66. Taylor D, Paton C, Kerwin R. *The Maudsley Prescribing Guidelines*. 9th edn. London: Informa Healthcare; 2007.

67. Mitchell AJ. Why don't patients take their medicine? Reasons and solutions in psychiatry. *Adv Psych Treat* 2007;**13**:336–46. http://dx.doi.org/10.1192/apt.bp.106.003194

68. Lewis SW, Barnes TRE, Davies L, Murray R, Dunn G, Hayhurst K, *et al.* Randomised controlled trial of effect of prescription of clozapine versus other second generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* 2006;**32**:715–23. http://dx.doi.org/10.1093/schbul/sbj067

69. Heinrichs DW, Hanlon TE, Carpenter WT. The quality of life scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984;**10**:388–98. http://dx.doi.org/10.1093/schbul/10.3.388

70. Khatri N, Romney DM, Pelletier G. Validity of self-reports about quality of life among patients with schizophrenia. *Psychiatr Serv* 2001;**52**:534–5. http://dx.doi.org/10.1176/appi.ps.52.4.534

71. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;**24**:67–74. http://dx.doi.org/10.1097/00005650-198601000-00007

72. Cramer JA, Rosenheck R, Xu W, Thomas J, Henderson W, Charney DS. Quality of life in schizophrenia: a comparison of instruments. *Schizophr Bull* 2000;**26**:659–66. http://dx.doi.org/10.1093/oxfordjournals.schbul.a033484

73. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;**13**:261–76. http://dx.doi.org/10.1093/schbul/13.2.261

74. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997;**58**:538–46. http://dx.doi.org/10.4088/JCP.v58n1205

75. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull* 2006;**32**:238–45. http://dx.doi.org/10.1093/schbul/sbj013

76. Galderisi G, Bucci P, Mucci A, Kirkpatrick B, Pini S, Rossi A, *et al.* Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. *Schizophr Res* 2013;**147**:157–62. http://dx.doi.org/10.1016/j.schres.2013.03.020

77. Marder SR, Kirkpatrick B. Defining and measuring negative symptoms of schizophrenia in clinical trials. *Eur Neuropsychopharmacol* 2014;**24**:737–43. http://dx.doi.org/10.1016/j.euroneuro.2013.10.016

78. Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H, Genetic Risk and Outcome of Psychosis (GROUP) Investigators. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *J Psychiatr Res* 2013;**47**:718–25. http://dx.doi.org/10.1016/j.jpsychires.2013.01.024

79. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry* 1993;**22**:39–44.

80. Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. Social Functioning Scale: the development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *Br J Psychiatry* 1990;**157**:853–9. http://dx.doi.org/10.1192/bjp.157.6.853

81. Tait L, Birchwood M, Trower P. A new scale (SES) to measure engagement with community mental health services. *J Mental Health* 2002;**11**:191–8. http://dx.doi.org/10.1080/09638230020023570-2

82. Ohlsen RI, Williamson RJ, Yusufi B, Mullan J, Irving D, Mukherjee S, *et al.* Interrater reliability of the Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS). *J Psychopharmacol* 2008;**22**:323–9. http://dx.doi.org/10.1177/0269881108091069

83. Simpson GM, Angus JWS. A rating scale for extrapyramidal side-effects. *Acta Psychiatr Scand Suppl* 1970;**212**:11–19. http://dx.doi.org/10.1111/j.1600-0447.1970.tb02066.x

84. Janno S, Holi MM, Tuisku K, Wahlbeck K. Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. *BMC Neurol* 2005;**5**:5. http://dx.doi.org/10.1186/1471-2377-5-5

85. Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989;**154**:672–6. http://dx.doi.org/10.1192/bjp.154.5.672

86. Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised Edition*. Washington, DC: US Department of Health, Education and Welfare; 1976.

87. National Institute for Health and Care Excellence. *Updated Guide to the Methods of Technology Appraisal, 2008*. London: National Institute for Health and Care Excellence; 2008.

88. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208. http://dx.doi.org/10.1016/0168-8510(90)90421-9

89. Al-Janabi H, Flynn T, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Qual Life Res* 2012;**21**:167–76. http://dx.doi.org/10.1007/s11136-011-9927-2

90. Personne M, Persson H, Sjöberg E. Citalopram toxicity. *Lancet* 1997;**350**:518–19. http://dx.doi.org/10.1016/S0140-6736(05)63109-1

91. Personne M, Sjöberg G, Persson H. Citalopram overdose: review of cases treated in Swedish hospitals. *J Toxicol Clin Toxicol* 1997;**35**:237–40. http://dx.doi.org/10.3109/15563659709001206

92. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 1. *J Psychosoc Nurs Ment Health Serv* 2011;**49**:13–16. http://dx.doi.org/10.3928/02793695-20111011-01

93. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 2. *J Psychosoc Nurs Ment Health Serv* 2011;**49**:13–16. http://dx.doi.org/10.3928/02793695-20111102-04

94. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Arch Gen Psychiatry* 1991;**48**:764–70. http://dx.doi.org/10.1001/archpsyc.1991.01810320088015

95. Lindenmayer J-P, Khan A, Iskander A, Abad MT, Parker B. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. *J Clin Psychiatry* 2007;**68**:368–79. http://dx.doi.org/10.4088/JCP.v68n0303

96. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *Br J Clin Pharmacol* 2000;**50**:166–71. http://dx.doi.org/10.1046/j.1365-2125.2000.00244.x

97. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trial. *Lancet* 2001;**357**:1191–4. http://dx.doi.org/10.1016/S0140-6736(00)04337-3

98. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal*. London: National Institute for Health and Care Excellence; 2013.

99. Medicines and Healthcare Products Regulatory Agency. *Citalopram and Escitalopram: QT Interval Prolongation. Drug Safety Update*. 2011. URL: www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation (accessed 9 February 2016).

100. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost-effectiveness Analysis in Health Care*. Oxford: Oxford University Press; 2011.

101. Hinkelman K, Yassourdis A, Kellner M, Jahn H, Wiedman K, Raedler TJ. No effects of antidepressants on negative symptoms in schizophrenia. *J Psychopharmacol* 2013;**33**:686–90. http://dx.doi.org/10.1097/JCP.0b013e3182971e68

102. Usall J, López-Carrilero R, Iniesta R, Roca M, Caballero M, Rodriguez-Jimenez R, *et al.* Double-blind, placebo-controlled study of the efficacy of reboxetine and citalopram as adjuncts to atypical antipsychotics for negative symptoms of schizophrenia. *J Clin Psychiatry* 2014;**75**:608–15. http://dx.doi.org/10.4088/JCP.13m08551

103. Shafti SS, Rey S, Abad A. Drug-specific responsiveness of negative symptoms. *Int J Psychosocial Rehab* 2005;**10**:43–51.

104. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophr Bull* 2010;**36**:359–69. http://dx.doi.org/10.1093/schbul/sbn094

105. Fervaha G, Foussias G, Agid O, Remington G. Amotivation and functional outcomes in early schizophrenia. *Psychiatry Res* 2013;**210**:665–8. http://dx.doi.org/10.1016/j.psychres.2013.07.024

106. Strauss GP, Horan WP, Kirkpatrick B, Fischer BA, Keller WR, Miski P, *et al.* Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res* 2013;**47**:783–90. http://dx.doi.org/10.1016/j.jpsychires.2013.01.015

107. Rocca P, Montemagni C, Zappia S, Piterà R, Sigaudo M, Bogetto F. Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting. *Psychiatry Res* 2014;**218**:284–9. http://dx.doi.org/10.1016/j.psychres.2014.04.018

108. Uhlenhuth EH, Alexander PE, Dempsey GM, Jones W, Coleman BS, Swiontek AM. Medication side effects in anxious patients: negative placebo responses? *J Affect Disord* 1998;**47**:183–90. http://dx.doi.org/10.1016/S0165-0327(97)00125-0

109. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, *et al.* American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* 2010;**121**:1047–60. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192704

110. Li EC, Esterly JS, Pohl S, Scott SD, McBride BF. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010;**30**:684–701. http://dx.doi.org/10.1592/phco.30.7.684

111. Leeson VC, Tyrer P. The advance of research governance in psychiatry: one step forward, two steps back. *Epidemiol Psychiatr Sci* 2013;**22**:313–20. http://dx.doi.org/10.1017/S2045796013000255

112. Vieweg WV, Hasnain M, Howland RH, Hettema JM, Kogut C, Wood MA, *et al.* Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *Am J Med* 2012;**125**:859–68. http://dx.doi.org/10.1016/j.amjmed.2011.12.002

113. Joint Formulary Committee. *British National Formulary*. 67th ed. London: BMJ Group and Pharmaceutical Press; 2014.

114. Curtis L. *Unit Costs of Health and Social Care 2014*. Canterbury: Personal Social Services Research Unit, University of Kent; 2014.

115. Department of Health. *Reference Costs 2013–14*. London: Department of Health; 2014.

116. Curtis L. *Unit Costs of Health and Social Care 2012*. Canterbury: Personal Social Services Research Unit, University of Kent; 2012.

117. NHS Choices. *Acupuncture*. 2014. URL: www.nhs.uk/conditions/acupuncture/Pages/Introduction.aspx (accessed 28 April 2014).

118. Plymouth Hospitals NHS Trust. *Private Healthcare Tariff. For Self-Pay Patients*. 2012. URL: www.plymouthhospitals.nhs.uk/patients%20and%20visitors/privatepatients/Documents/PHNTPrivateHealthcareTariff201112SelfPay.pdf (accessed 17 July 2014).

119. ISD Scotland. *Scottish National Tariff 2013/2014*. 2014. URL: www.isdscotland.org/Health-Topics/Finance/Costs/File-Listings-2014.asp (accessed 18 July 2014).

120. Office for National Statistics. *Annual Survey of Hours and Earnings, 2012 Revised Results*. 2013. URL: www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-328218 (accessed 21 July 2014).

Appendix 1 Completeness of follow-up data in the two treatment groups

Follow-up assessment	Placebo ($n = 32$)	Citalopram ($n = 30$)
Week 12	25	24
Week 36	24	22
Week 48	23	19

Appendix 2 Corrected QT interval for patients who complied fully with study, recording data at baseline, 12, 36 and 48 weeks

	Treatment group		Difference between groups (95% CI)
	Placebo ($n = 9$)	Citalopram ($n = 5$)	
QTc at baseline, mean (milliseconds) (SD)	387.1 (24.9)	397.5 (13.2)	–10.4 (–36.8 to 16.0)
QTc at week 12, mean (milliseconds) (SD)	388.9 (22.9)	396.6 (17.7)	–7.6 (–33.5 to 18.3)
QTc at week 36, mean (milliseconds) (SD)	392.7 (18.1)	415.8 (16.1)	–23.1 (–44.3 to –1.8)
QTc at week 48, mean (milliseconds) (SD)	394.9 (14.5)	390.3 (14.8)	4.6 (–13.2 to 23.4)

Appendix 3 Health economics data availability

	Baseline	12 weeks	36 weeks	48 weeks
Any data, *n*	60	48	44	40
EQ-5D-3L, *n*	60	47	44	40
ICECAP-A, *n*	59	47	44	40
Trial medication, *n*	55	44	36	34
Non-trial medication, *n*	59	46	41	28
Other resource use, *n*	60	46	44	40

Appendix 4 Types of the health-care, social care and voluntary sector services

TABLE 12 Types of the health-care, social care and voluntary sector services used by any of the patients in the ACTIONS study and their respective UK national-level unit costs with source information. Unit costs (in £ for year 2013–14)

Resource use	Unit costs (£)	Unit	Source of estimate
Medication			
Oral medication	Various	Per daily dose (mg)	BNF 67[113]
Depot medication	Various	Per administered depot (ml/mg)	BNF 67[113]
Mental health community/outpatient			
Community mental health nurse – telephone contact	6.60	Per contact	Curtis (2014)[114]
Community mental health nurse – face-to-face contact in NHS setting	16.50	Per visit	Curtis (2014)[114]
Community mental health nurse – face-to-face contact in community	34.65	Per visit	Curtis (2014)[114]
Psychiatrist – telephone contact	28.45	Per contact	NHS Reference Costs,[115] Curtis (2014)[114]
Psychiatrist – face-to-face contact in NHS setting	47.00	Per visit	NHS Reference Costs,[115] Curtis (2014)[114]
Psychiatrist – face-to-face contact in community	117.5	Per visit	NHS Reference Costs,[115] Curtis (2014)[114]
Psychologist – telephone contact	16.33	Per contact	Curtis (2014)[114]
Psychologist – face-to-face contact in NHS setting	138.00	Per visit	Curtis (2014)[114]
Psychologist – face-to-face contact in community	173.88	Per visit	Curtis (2014)[114]
Drug/alcohol service worker – telephone contact	29.05	Per contact	Curtis (2014)[114]
Drug/alcohol service worker – face-to-face contact in NHS setting	48.00	Per visit	Curtis (2014)[114]
Drug/alcohol service worker – face-to-face contact in community	120.00	Per visit	Curtis (2014)[114]
Care co-ordinator – telephone contact	9.68	Per contact	Curtis (2014)[114]
Care co-ordinator – face-to-face contact in NHS setting	80.8	Per visit	Curtis (2014)[114]
Care co-ordinator – face-to-face contact in community	101.8	Per contact	Curtis (2014)[114]
Other secondary care worker (e.g. occupational therapist) – telephone contact	8.77	Per contact	Curtis (2014)[114]
Other secondary care worker (e.g. occupational therapist) – face-to-face contact in NHS setting	74.13	Per visit	Curtis (2014)[114]
Other secondary care worker (e.g. occupational therapist) – face-to-face contact in community	93.40	Per visit	Curtis (2014)[114]
Day centre (groups/programmes, non-health-care staff)	38.2	Per session	Curtis (2012) – inflated[116]

continued

TABLE 12 Types of the health-care, social care and voluntary sector services used by any of the patients in the ACTIONS study and their respective UK national-level unit costs with source information. Unit costs (in £ for year 2013–14) (*continued*)

Resource use	Unit costs (£)	Unit	Source of estimate
Drop-in centre (including street agencies) (informal)	38.2	Per session	Curtis (2012) – inflated[116]
Self-help group/support group	60.91	Per session	Curtis (2012) – inflated[116]
Mental health inpatient			
Psychiatric hospital inpatient general ward	348.93	Per day	Curtis (2012) – inflated[116]
Non-mental health outpatient			
Alternative therapies (NHS) – face-to-face contact in NHS setting	43.75	Per visit	NHS Choices[117]
Alternative therapies (private) – face-to-face contact in private health-care facility	69.17	Per visit	Private Healthcare Tariff (2012)[118]
Paramedic ambulance see and treat or refer	179.54	Per contact	NHS Reference Costs[115]
Day patient hospital attendance/accident and emergency attendance	135.12	Per attendance	NHS Reference Costs[115]
Other medical/surgical outpatient visits	3.00–219.81	Per visit	NHS Reference Costs[115]
Non-mental health inpatient			
Other medical/surgical inpatient department	466.27	Per day	Scottish National Tariff 2013/2014[119]
Primary care			
GP – telephone contact	23.00	Per contact	Curtis (2014)[114]
GP – face-to-face contact in NHS setting	39.00	Per visit	Curtis (2014)[114]
GP – face-to-face contact in community	96.06	Per visit	Curtis (2014)[114]
Practice nurse – telephone contact	4.40	Per contact	Curtis (2014)[114]
Practice nurse – face-to-face contact in NHS setting	11.00	Per visit	Curtis (2014)[114]
Practice nurse – face-to-face contact in community	23.10	Per visit	Curtis (2014)[114]
District nurse – face-to-face contact in NHS setting	37.00	Per visit	Curtis (2014)[114]
District nurse – face-to-face contact in community	46.62	Per visit	Curtis (2014)[114]
Other primary care worker (e.g. dietician or nutritionist) – face-to-face contact in NHS setting	80.39	Per visit	NHS Reference Costs[115]
Social care			
Community support worker – telephone contact	3.33	Per contact	Curtis (2014)[114]
Community support worker – face-to-face contact in NHS setting	6.67	Per visit	Curtis (2014)[114]
Community support worker – face-to-face contact in community	8.84	Per visit	Curtis (2014)[114]
Social worker – telephone contact	26.84	Per contact	Curtis (2012) – inflated[116]
Social worker – face-to-face contact in NHS setting	53.68	Per visit	Curtis (2012) – inflated[116]
Social worker – face-to-face contact in community	68.48	Per visit	Curtis (2014)[114]
Home help/home care worker – telephone contact	6.17	Per contact	Curtis (2014)[114]
Home help/home care worker – face-to-face contact in NHS setting	27.75	Per visit	Curtis (2014)[114]

TABLE 12 Types of the health-care, social care and voluntary sector services used by any of the patients in the ACTIONS study and their respective UK national-level unit costs with source information. Unit costs (in £ for year 2013–14) (*continued*)

Resource use	Unit costs (£)	Unit	Source of estimate
Home help/home care worker – face-to-face contact in community	27.75	Per visit	Curtis (2014)[114]
Housing worker – telephone contact	2.64	Per contact	Assuming national average salary, ONS (2013)[120]
Housing worker – face-to-face contact in NHS setting	5.29	Per visit	Assuming national average salary, ONS (2013)[120]
Housing worker – face-to-face contact in community	6.66	Per visit	Assuming national average salary, ONS (2013)[120]
Voluntary/charity worker (e.g. advocacy) – telephone contact	2.64	Per contact	Assuming national average salary, ONS (2013)[120]
Voluntary/charity worker (e.g. advocacy) – face-to-face contact in NHS setting	5.29	Per visit	Assuming national average salary, ONS (2013)[120]
Voluntary/charity worker (e.g. advocacy) – face-to-face contact in community	6.66	Per visit	Assuming national average salary, ONS (2013)[120]
Indirect costs			
Lost productivity (sick leave)	116.8	Per day	Assuming national average salary, ONS (2013)[120]
Informal care	15.6	Per hour	Assuming national average salary, ONS (2013)[120]

ONS, Office for National Statistics.

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