

Amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS): a double-blind, placebo-controlled, randomised trial of clinical effectiveness and cost-effectiveness

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**National Institute for
Health Research**

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Abstract

Amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS): a double-blind, placebo-controlled, randomised trial of clinical effectiveness and cost-effectiveness

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Background: When treatment-refractory schizophrenia shows an insufficient response to a trial of clozapine, clinicians commonly add a second antipsychotic, despite the lack of robust evidence to justify this practice.

Objectives: The main objectives of the study were to establish the clinical effectiveness and cost-effectiveness of augmentation of clozapine medication with a second antipsychotic, amisulpride, for the management of treatment-resistant schizophrenia.

Design: The study was a multicentre, double-blind, individually randomised, placebo-controlled trial with follow-up at 12 weeks.

Settings: The study was set in NHS multidisciplinary teams in adult psychiatry.

Participants: Eligible participants were people aged 18–65 years with treatment-resistant schizophrenia unresponsive, at a criterion level of persistent symptom severity and impaired social function, to an adequate trial of clozapine monotherapy.

Interventions: Interventions comprised clozapine augmentation over 12 weeks with amisulpride or placebo. Participants received 400 mg of amisulpride or two matching placebo capsules for the first 4 weeks, after which there was a clinical option to titrate the dosage of amisulpride up to 800 mg or four matching placebo capsules for the remaining 8 weeks.

Main outcome measures: The primary outcome measure was the proportion of 'responders', using a criterion response threshold of a 20% reduction in total score on the Positive and Negative Syndrome Scale.

Results: A total of 68 participants were randomised. Compared with the participants assigned to placebo, those receiving amisulpride had a greater chance of being a responder by the 12-week follow-up (odds ratio 1.17, 95% confidence interval 0.40 to 3.42) and a greater improvement in negative symptoms, although neither finding had been present at 6-week follow-up and neither was statistically significant. Amisulpride was associated with a greater side effect burden, including cardiac side effects. Economic analyses indicated that amisulpride augmentation has the potential to be cost-effective in the short term [net saving of between £329 and £2011; no difference in quality-adjusted life-years (QALYs)] and possibly in the longer term.

Limitations: The trial under-recruited and, therefore, the power of statistical analysis to detect significant differences between the active and placebo groups was limited. The economic analyses indicated high uncertainty because of the short duration and relatively small number of participants.

Conclusions: The risk–benefit of amisulpride augmentation of clozapine for schizophrenia that has shown an insufficient response to a trial of clozapine monotherapy is worthy of further investigation in larger studies. The size and extent of the side effect burden identified for the amisulpride–clozapine combination may partly reflect the comprehensive assessment of side effects in this study. The design of future trials of such a treatment strategy should take into account that a clinical response may not be evident within the 4- to 6-week follow-up period usually considered adequate in studies of antipsychotic treatment of acute psychotic episodes. Economic evaluation indicated the need for larger, longer-term studies to address uncertainty about the extent of savings because of amisulpride and impact on QALYs. The extent and nature of the side effect burden identified for the amisulpride–clozapine combination has implications for the nature and frequency of safety and tolerability monitoring of clozapine augmentation with a second antipsychotic in both clinical and research settings.

Trial registration: EudraCT number 2010-018963-40 and Current Controlled Trials ISRCTN68824876.

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List of abbreviations

AIMS	Abnormal Involuntary Movement Scale	GP	general practitioner
AMICUS	amisulpride augmentation in clozapine-unresponsive schizophrenia trial	HTA	Health Technology Assessment
ANNSERS	Antipsychotic Non-Neurological Side Effects Scale	ICER	incremental cost-effectiveness ratio
ANNSERS-E	Antipsychotic Non-Neurological Side Effects Scale – Enhanced Version	IQR	interquartile range
BARS	Barnes Akathisia Rating Scale	NB	net benefit
BMI	body mass index	NHS EED	NHS Economic Evaluation Database
BPRS	Brief Psychiatric Rating Scale	NICE	National Institute for Health and Care Excellence
CDSS	Calgary Depression Rating Scale for Schizophrenia	NIHR	National institute for Health Research
CEAC	cost-effectiveness acceptability curve	OR	odds ratio
CGI	clinical global impression	PANSS	Positive and Negative Syndrome Scale
CI	confidence interval	POMH-UK	Prescribing Observatory for Mental Health
CONSORT	Consolidated Standards of Reporting Trials	QALY	quality-adjusted life-year
DMEC	Data Monitoring and Ethics Committee	RCT	randomised controlled trial
ECG	electrocardiogram	SAI	Schedule for the Assessment of Insight
EPQ	economic patient questionnaire	SD	standard deviation
EPS	extrapyramidal side effect	SES	Service Engagement Scale
EPSE	Extrapyramidal Side Effects Scale	SOFAS	Social and Occupational Functioning Assessment Scale
EQ-5D-3L	EQ-5D three levels	VAS	visual analogue scale
		WTPT	willingness-to-pay value threshold

Plain English summary

When schizophrenia has not improved with standard antipsychotic medication, a particular antipsychotic (clozapine) can sometimes work. If the response to treatment with clozapine on its own is insufficient, a second antipsychotic is sometimes added. However, despite several research studies addressing such a combination treatment, it is still uncertain whether or not it is worthwhile trying in clinical practice. Therefore, we carried out a trial comparing the effects of adding either an antipsychotic (amisulpride) or a dummy tablet (placebo) for 12 weeks in people with schizophrenia who had not been helped much by their clozapine treatment. We chose amisulpride because the way this medicine works may be complementary to that of clozapine, and it is less likely than some other antipsychotics to add to some of the characteristic side effects of clozapine, such as sedation, weight gain and changes in the levels of blood sugar and fats.

To avoid bias towards either amisulpride or placebo, no one knew which of these two medications any person was prescribed. Those people prescribed amisulpride proved to be a little more likely than those given placebo to have a 20% improvement in their symptoms by the end of the 12-week trial, although we did not manage to enrol enough people in our trial to be confident about this finding. More side effects, including heart symptoms, were reported by the people given the amisulpride and clozapine combination, which suggests that this treatment should be carefully monitored for safety and tolerability in both clinical and research settings.

Scientific summary

Background

In around one-third of people with schizophrenia, the illness shows a poor response to standard treatment with antipsychotic medication. Clozapine is the only antipsychotic drug for which there is convincing evidence of efficacy in such treatment-resistant illness, but its effectiveness is limited, as only around one-third of patients will show an adequate response to the drug. When a trial of clozapine proves to be ineffective or only partially effective, clinicians commonly add a second antipsychotic, although a robust evidence base to justify this practice, with regard to the potential benefits and risks, is lacking.

Objectives

The main objectives of the study were to test the benefits, costs and risks of augmenting clozapine with amisulpride, compared with placebo, for treatment-resistant schizophrenia that had also proved to be relatively unresponsive to clozapine. Secondary aims were to add to the clinical and economic evidence base for clozapine augmentation with a second-generation antipsychotic and provide evidence relating to the duration of an adequate trial of clozapine augmentation.

Design

The amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS) study was a multicentre, double-blind, individually randomised, placebo-controlled, parallel-arm randomised controlled trial (RCT), with a 12-week follow-up. The target symptoms and/or behaviours that characterised the participants' clinical presentations at baseline were identified. Therapeutic improvement was assessed in terms of overall symptom severity, but also using broader, clinically relevant outcome measures of social and occupational function as well as overall health status and utility. Side effects were systematically investigated, including the use of a scale designed to comprehensively assess the full range of adverse effects of antipsychotic medication.

Setting

The study was set in NHS multidisciplinary teams in adult psychiatry, treating people with schizophrenia who are prescribed clozapine.

Participants

Eligible participants were people aged 18–65 years with a treatment-resistant schizophrenic illness that was relatively unresponsive, at a criterion level of persistent symptom severity and impaired social function, to a trial of clozapine monotherapy.

Interventions

Study interventions comprised clozapine augmentation with another second-generation antipsychotic, amisulpride, or placebo over 12 weeks. Participants received 400 mg of amisulpride or two matching

placebo capsules for the first 4 weeks, after which there was a clinical option to titrate the dosage of amisulpride up to 800 mg or four matching placebo capsules for the remaining 8 weeks.

Main outcome measures

The primary outcome measure was the proportion of 'responders' using a recognised criterion response threshold of a 20% reduction in total score on the Positive and Negative Syndrome Scale, reflecting an improvement in mental state.

Results

Sixty-eight participants were randomised. The trial under-recruited and, therefore, the power of statistical analysis to detect significant differences between the active and placebo groups was limited. Compared with those participants assigned to placebo, those in the amisulpride treatment arm had a greater chance of being a responder by the 12-week follow-up [odds ratio 1.17, 95% confidence interval (CI) 0.40 to 3.42]. There was also the suggestion of a greater improvement in negative symptoms. Neither finding had been present at 6-week follow-up and neither was statistically significant. Amisulpride was also associated with a greater side effect burden, including cardiac side effects.

The results from the economic evaluation suggest that amisulpride augmentation may be cost saving in the short-term (net saving £1816, standard deviation £369; 95th percentiles –£2540 to £1092). However, the 95th percentiles indicate that amisulpride augmentation may also increase costs. There was no clear difference in overall health (as measured by quality-adjusted life-years). Although the extent of any savings is uncertain, the cost-effectiveness acceptability analysis indicated a high probability that amisulpride augmentation is cost-effective. The results from the economic model are more uncertain, but suggest that over the longer time frame of 1 year, amisulpride may still be cost-effective.

Conclusions

The limited benefit of amisulpride seen in this trial challenges the rationale of potent D₂ dopamine receptor blockade as a criterion for selecting an augmenting antipsychotic to treat clozapine-unresponsive illness. Nevertheless, the findings suggest that the risk–benefit of amisulpride augmentation of clozapine for schizophrenia that has shown an insufficient response to a trial of clozapine monotherapy is still worthy of further investigation in larger studies. The size and extent of the side effect burden identified for the amisulpride–clozapine combination may partly reflect the thorough assessment of side effects in this study, which was more systematic and comprehensive than is generally conducted in clinical trials of antipsychotics. Health economic analyses suggested that amisulpride augmentation has the potential to be cost-effective in the short term and possibly in the longer term.

Future research

The design of future trials of such a treatment strategy should take into account the fact that a clinical response may not be evident within the 4- to 6-week follow-up period usually considered adequate in studies of antipsychotic treatment of acute psychotic episodes. The extent and nature of the side effect burden identified for the amisulpride–clozapine combination has implications for the nature and frequency of safety and tolerability monitoring of clozapine augmentation with a second antipsychotic in both clinical and research settings. Longer-term prospective RCTs of amisulpride augmentation would be necessary to establish the cost-effectiveness of this pharmacological strategy, but whether or not such trials are feasible in the UK remains uncertain, given the continuing challenge of recruitment in mental health studies in the NHS.

Trial registration

This trial is registered as EudraCT 2010-018963-40 and ISRCTN68824876.

Funding

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

Chapter 1 Introduction

In around one-third of people with schizophrenia, the illness shows a poor response to standard treatment with antipsychotic medication. Although a relatively small proportion will fail to achieve remission even after the first exposure to antipsychotic medication, with either first- or second-generation drugs,¹ more commonly the illness becomes progressively more unresponsive to medication with subsequent relapses.^{2,3} This treatment-resistant subgroup of patients represents a major clinical challenge in everyday psychiatry, and consumes a disproportionate amount of NHS funding.⁴⁻⁶ Mangalore and Knapp⁷ estimated that the total societal cost of schizophrenia in the UK in 2004/5 was £6.7B. The direct cost of treatment and care, falling on the UK public purse, was around £2B, whereas the burden of indirect costs to society was approaching £4.7B. The cost of informal care and private expenditures by families and carers was around £615M, whereas the loss of productivity as a result of unemployment, absence from work and premature mortality of people with schizophrenia was estimated to be £3.4B and the lost productivity of their carers estimated to be around £32M. Furthermore, Mangalore and Knapp⁷ calculated that, in addition to costs to the criminal justice system, around £570M was being paid out in benefit payments, associated with about £14M administration costs. Treatment-resistant illness is considered to be more costly, usually requiring longer-term residential and intensive community treatments. There is clinical and economic need to evaluate treatments to improve outcomes in this group of patients.

Clozapine augmentation with a second antipsychotic

For treatment-resistant schizophrenia, a common therapeutic approach is to use more than one antipsychotic, although a robust evidence base to justify this is lacking. Recent surveys of prescribing patterns in the USA suggest that about 15% of outpatients and up to 50% of inpatients with schizophrenia receive two or more antipsychotics.⁸ In the UK in 2012, national clinical audit data from the Prescribing Observatory for Mental Health (POMH-UK) on over 5000 acute inpatients and over 3000 forensic patients prescribed antipsychotics revealed regularly prescribed combined antipsychotics in 14% and 17%, respectively.⁹ A common reason given by clinical teams for prescribing such a combination was failure of the illness to respond to treatment with a single antipsychotic. In the POMH-UK audit, just under 5% of prescriptions for combined antipsychotics in acute adult wards represented the augmentation of clozapine with another antipsychotic, whereas in rehabilitation/complex needs services and forensic services the respective figures were in excess of 20%. These figures are in line with other reports of the prevalence of clozapine augmentation, ranging from 18% to 44% depending on the clinical setting and country.¹⁰⁻¹² In summary, it seems that around one-third of all clozapine-treated patients receive augmentation with another antipsychotic.¹³ This is because it is one of the few therapeutic strategies available to clinicians for those people with schizophrenia that has proved to be poorly responsive to clozapine.

Clozapine is the only antipsychotic for which there is convincing evidence of efficacy in strictly defined treatment-resistant schizophrenia, but in such cases it has limited effectiveness, with 30–40% of patients showing an inadequate response to the drug.¹⁴ In some patients, a range of potentially serious side effects such as seizures, sedation and tachycardia may prevent the optimal dose being reached. In addition, weight gain and metabolic side effects that increase the risk of diabetes and cardiovascular disease become apparent in many.

In an attempt to improve efficacy and limit tolerability problems, clinicians commonly augment clozapine with another antipsychotic, despite limited evidence on the potential risks and benefits of this practice.¹⁵ In 2005, Kontaxakis *et al.*¹⁶ identified 15 case studies, with a total of 33 patients, of adjunctive agents in clozapine-resistant schizophrenia, 10 of which involved a second antipsychotic (eight using risperidone, one using sulpiride and one using olanzapine). They concluded that various methodological shortcomings

limited the impact of the findings. These authors came to a similar conclusion after conducting a critical review of 11 randomised controlled trials (RCTs; with a total of 270 participants) of clozapine augmentation in treatment-resistant schizophrenia,¹⁷ in only one of which was an antipsychotic (sulpiride) used as the adjunctive medication. Methodological weaknesses included the fact that only one trial adequately reported the dose and duration of the clozapine monotherapy phase. Similarly, Remington *et al.*¹⁵ noted that the current body of evidence for clozapine augmentation consisted of data from a limited number of small open trials and case series reports. But they suggested that systematic research was warranted and argued for detailed cost–benefit analysis. Buckley *et al.*¹¹ agreed, stating that there was ‘a dearth of double-blind studies’, and concluded that these adjunctive therapies were worthy of further testing in carefully controlled clinical trials.

The subsequent publication of several new open studies and small RCTs testing the therapeutic value of augmenting clozapine with another antipsychotic prompted us to conduct a meta-analysis of eligible RCTs.¹⁸ A systematic literature search identified eight open studies and four eligible RCTs in which clozapine was augmented with a second antipsychotic, with a total of 166 participants. The two RCTs that had lasted 10 weeks or more gave an odds ratio (OR) of response to treatment of 4.41 [95% confidence interval (CI) 1.38 to 14.07]. We concluded that for clozapine-refractory schizophrenia, augmentation of clozapine with another antipsychotic drug is worthy of an individual clinical trial, but this may need to be longer than the 4–6 weeks usually recommended for acute antipsychotic monotherapy, a view supported by Correll *et al.*¹⁹ Mouaffak *et al.*¹³ noted that the discrepant results of the published studies of clozapine augmentation with another antipsychotic; they identified methodological shortcomings that related to the heterogeneity of definitions of resistance to clozapine, choice of outcome measures, and the dose and duration of the adjunctive drugs, which they considered ‘a major limitation for drawing conclusions’. Clinical response in such studies has generally been defined as a 20% reduction in total score on the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS). Both the BPRS and the PANSS assess a broad range of symptoms, including both positive symptoms (e.g. delusions, hallucinations and thought disorder) and negative symptoms (e.g. blunted affect and emotion, poverty of speech, lack of motivation, and social and emotional withdrawal).

The updated National Institute for Health and Care Excellence (NICE) 2009 guideline for the treatment of schizophrenia²⁰ supported the augmentation of clozapine with a second antipsychotic in patients with an inadequate response to clozapine alone; advice that was in accord with our own meta-analysis.¹⁸ After the publication of our meta-analysis, data became available for four further, short-term, clozapine augmentation RCTs, one each for risperidone²¹ and haloperidol,²² and two using aripiprazole,^{23,24} a medicine that has a different pharmacology to other antipsychotic drugs in that it is a D₂ partial agonist. All four studies were reported as negative, although the trial by Chang *et al.*²³ showed a statistically significant advantage for augmentation with aripiprazole in regard to a reduction in negative symptom score.

By 2012, Sommer *et al.*²⁵ were able to identify 10 RCTs of augmentation of clozapine with a second antipsychotic and found only modest or absent efficacy. Also in 2012, Taylor *et al.*²⁶ conducted a meta-analysis of 14 such studies. These investigators were more positive about this strategy for clozapine-refractory illness, concluding from their findings that augmentation of clozapine with a second antipsychotic was modestly superior to placebo and equally well tolerated. Looking at effect size by treatment duration, they found no significant relationship between duration of treatment and reduction in symptoms. In other words, there was no confirmation of the earlier suggestion that longer trials might produce relatively more robust outcomes for adding a second antipsychotic.

Risks of clozapine augmentation

When adding one drug to another it is important to consider any potential 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 or

pharmacodynamic, where one drug enhances or opposes the pharmacological action of the other. Case reports have described clinically significant elevations in serum clozapine levels after augmentation with the second-generation antipsychotic, risperidone.²⁷ The potential clinical relevance of such a pharmacokinetic effect is, first, that it could cause clozapine plasma levels to reach an individual patient's threshold level for response, a benefit that might be erroneously attributed to a pharmacodynamic synergy between clozapine and the augmenting drug. Second, the increased clozapine plasma levels could be associated with the development of serious dose-related side effects. However, clozapine levels had been systematically measured before and after antipsychotic augmentation in four^{23,28–30} of the clozapine-augmentation RCTs included in our meta-analysis,⁸ and in one of these RCTs³⁰ the clozapine metabolite norclozapine was also measured and no significant changes in mean plasma clozapine levels were reported.

In terms of side effects, RCTs and open studies have found clozapine augmentation with a second antipsychotic to be relatively well tolerated. The main treatment-emergent side effects have been predictable from pharmacology of the augmenting drug, with extrapyramidal side effects (EPSs) and prolactin elevation being the most common problems. However, there are isolated case reports of more serious side effects. Published case reports of clozapine augmentation with risperidone have noted agranulocytosis, atrial ectopic beats and possible neuroleptic malignant syndrome,^{31–33} whereas case reports of clozapine augmentation with aripiprazole have mentioned nausea, vomiting, insomnia, headache and agitation in the first 2 weeks,³⁴ tachycardia²³ and also modest weight loss.^{34,35} Clozapine itself is commonly associated with sedation, weight gain and postural hypotension. Any augmenting antipsychotic should ideally have a low propensity to compound these side effects.

In summary, the studies of augmentation of clozapine with a second antipsychotic for schizophrenic illness that has shown an insufficient response to clozapine have shown only modest improvements in overall symptom severity that may take 10 weeks to be evident. No particular augmenting antipsychotic has been shown to be consistently superior to any other. Any benefit seen is not obviously attributable to pharmacokinetic interaction: clozapine and norclozapine levels have not been found to be significantly raised in studies when measured. The augmenting antipsychotic drugs tested have generally not been systematically assessed for compounding clozapine side effects (e.g. sedation, weight gain, metabolic side effects) or problems such as akathisia or significant elevations in serum prolactin. Furthermore, any uncommon but severe side effects with this strategy are unlikely to have been detected in the relatively small studies conducted thus far.

Amisulpride augmentation of clozapine

Despite the lack of robust clinical evidence on the potential risks and benefits of clozapine augmentation with amisulpride, this is a strategy commonly used by clinicians in the NHS. The POMH-UK clinical data from 2012⁹ revealed that amisulpride was the antipsychotic most commonly prescribed in association with clozapine.

Amisulpride has been tested in case reports and case series^{36–38} and open studies of clozapine augmentation.^{39–41} Augmentation with amisulpride was found to be well tolerated, and clinical responses (again defined as a $\geq 20\%$ reduction on PANSS total score) in the open studies by Munro *et al.*⁴⁰ and Ziegenbein *et al.*³⁹ occurred in around 70% of patients. Hotham *et al.*⁴² augmented clozapine with amisulpride in six forensic (high-secure) patients and reported a reduction in aggression and violence. There has been one previous pilot, double-blind, placebo-controlled RCT of clozapine augmentation with amisulpride⁴³ for 6 weeks in 16 patients, with established schizophrenia, who were partially responsive to clozapine. The primary outcome measures, such as reduction in BPRS total score, failed to show a significant improvement, which the investigators attributed to the study's lack of power.

Study aims

The main aims of the study were:

- to test the benefits, costs and risks of augmenting clozapine with amisulpride compared with placebo
- to add to the clinical and economic evidence base for clozapine augmentation with a second-generation antipsychotic
- to examine the potential benefits, costs and risks of clozapine augmentation in treatment-resistant schizophrenia.

The key aim of the economic analysis was to assess whether or not augmenting clozapine with amisulpride was likely to be cost-effective. To address this aim, two sets of analyses were conducted. The first set used the trial data set (within-trial analyses) and the 3-month, scheduled, follow-up period to:

- estimate the use of health- and social-care services to manage participants who were treated with clozapine and placebo and those who had clozapine plus amisulpride
- estimate the direct costs of health- and social-care services to manage participants who were treated with clozapine and placebo and those who had clozapine plus amisulpride
- estimate the overall health status of participants who had clozapine and placebo and those who were treated with clozapine plus amisulpride
- estimate the utility and quality-adjusted life-years (QALYs) of participants who were treated with clozapine and placebo and those who had clozapine plus amisulpride
- estimate the net costs, QALYs and incremental cost per QALY gained associated with augmenting clozapine with amisulpride.

The second set of analyses used an economic model to explore the following questions over the longer term:

- What are the likely net costs, QALYs and incremental cost per QALY gained, if symptom response of augmenting clozapine with amisulpride increases/decreases in the long term?
- What are the likely net costs, QALYs and incremental cost per QALY gained, if augmenting clozapine with amisulpride is associated with increased/decreased side effects in the long term?

Chapter 2 Methods

Trial design

The study was a randomised, double-blind, placebo-controlled trial lasting 12 weeks. Eligible patients, all receiving continuing clozapine treatment, were randomised 1 : 1 to receive augmentation with either amisulpride or placebo. Researchers, participants and care providers were blinded to patients' treatment randomisation until the end of their participation by the use of identically matched placebo medicine. The trial recruited from November 2011 to December 2014.

Sample size

In previous augmentation studies of clozapine with a second antipsychotic lasting ≥ 10 weeks, 35%²⁸ and 50%⁴⁴ of the actively augmented arm responded compared with 10% in those augmented with placebo. Response was defined as a $> 20\%$ improvement on the BPRS or PANSS. To detect a more conservative response of 30% in our amisulpride arm and 10% in the placebo arm, with 90% power and an alpha of 0.05, we required 92 participants per group (two-sided). Using existing continuous data, detecting an effect size of 0.5 BPRS score standard deviations (SDs; compared with the final placebo group mean BPRS score) would require 85 participants per arm. This held whether we used the results from Josiassen *et al.*²⁸ [mean BPRS: 44.7 (placebo) vs. 40.1 (active arm), SD 9.2] or Shiloh *et al.*⁴⁴ [mean BPRS: 41.2 (placebo) vs. 35.1 (active), SD 12.2], both using 90% power and a two-sided alpha of 0.05.

The plan was to randomise 230 patients (including 20% inflation for drop-outs) on clozapine 1 : 1 to receive augmentation with placebo or amisulpride. Clinical protocols for the use of clozapine involve regular attendance for haematological testing and most patients either are inpatients or attend clozapine clinics. Once stabilised on treatment, the attrition rate is low. Small studies of clozapine augmentation report completion rates of $> 80\%$, so we estimated there would be 184 study completers (i.e. 92 completers in each treatment group).

Our sample size calculation was based on results from previous studies.^{28,44} These studies were comparable with the proposed study in terms of length of follow-up, intervention used and proposed primary outcome. From these we based our sample size on 30% of participants in the amisulpride arm of the trial achieving a $> 20\%$ improvement on the BPRS or on the PANSS, which is slightly lower than those shown in the literature.^{28,44} Therefore, it was expected that there would be a large difference in the percentage achieving such a threshold level of improvement on the BPRS or on the PANSS between the amisulpride and placebo groups at the end of follow-up, and so there was no statistical justification for increasing the sample size.

As part of the amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS) study rescue plan submitted to the Health Technology Assessment (HTA) programme in March 2013, the sample size was recalculated with the same assumptions but with 80% power. This gave 72 participants in each arm (144 in total); accounting for 20% drop-out, the revised target was 90 participants in each group (180 participants in total). This was a pragmatic decision to determine the sample size needed while maintaining power at an acceptably high level.

Primary outcomes

The primary outcome measure was the proportion of patients with a criterion response threshold of a 20% reduction in total PANSS score. This is a commonly used criterion for therapeutic response in schizophrenia trials, which allows for comparison with other published trials¹⁸ and inclusion of the study results in any appropriate systematic review or meta-analysis. The PANSS^{45,46} is a 30-item rating scale designed to provide a comprehensive assessment of psychopathology in adult patients with schizophrenia.

Inter-rater reliability

Following initial training sessions on the PANSS for the study researchers, the reliability of PANSS ratings by researchers across the various research sites was formally tested. Sixteen researchers were asked to independently rate the same PANSS interview (video of an actor). The intraclass correlation for individual items was 0.63 (moderate agreement) and subscales at 0.86 (substantial agreement). Discrepancies on the ratings of scale items between the researchers who had taken part were then reviewed and discussed with them, in order to further improve the reliability of the ratings.

Secondary outcomes

Negative symptoms

The PANSS negative symptom subscale score was used to assess negative symptoms. The validity and reliability of this negative subscale have been established.^{47,48}

Social and occupational function

Impact on social and occupational function was measured using the Social and Occupational Functioning Assessment Scale (SOFAS),⁴⁹ which was derived from the Global Assessment Scale but more focused on a patient's social and occupational functioning; for an impairment to be rated, it must relate to psychological problems not lack of opportunity. Note that higher scores on the SOFAS indicate a better level of functioning.

Treatment-refractory, target symptoms or behaviours

As part of the final assessment of eligibility for each participant, the PANSS and SOFAS assessments were reviewed with members of the participant's clinical team. The team was asked to identify up to three critical, target symptoms and/or behaviours that were refractory to treatment; these were phenomena that had proved to be persistent and were judged clinically to have made a major adverse impact on the participant's social function and community reintegration, been a major cause of psychological distress and/or precluded discharge from hospital.

Service engagement

The level of engagement with clinical services was assessed using the Service Engagement Scale (SES),⁵⁰ a 14-item measure consisting of statements that assess client engagement with services, rated on a 4-point Likert scale from 'not at all or rarely' to 'most of the time'. Four subscales assess availability, collaboration, help-seeking and treatment adherence. High internal consistency and retest reliability, including discrimination between criterion groups, have been demonstrated for the SES in a community setting.⁵⁰

Depression

Depressive symptoms were assessed using the Calgary Depression Rating Scale for Schizophrenia (CDSS),⁵¹ a scale designed to minimise the potentially confounding symptom overlap between depressive features and both negative symptoms and EPSs.

Insight

Insight was assessed using the Schedule for the Assessment of Insight (SAI).⁵² This scale comprises a semistructured interview that obtains measures of three dimensions of insight: (1) awareness of mental

illness, scored 0–6; (2) the ability to correctly attribute psychotic experiences, scored 0–4; and (3) acceptance of the need for treatment, scored 0–4. The maximum total score on the three dimensions is 14, but the scale also includes a supplementary question on hypothetical contradiction, scored 0–4. Thus, the maximum total score for the scale is 18, which indicates full insight.

Side effects

The Antipsychotic Non-Neurological Side Effects Scale (ANNSERS)⁵³ has 44 clinician-judged items with good inter-rater reliability. It was designed to systematically and comprehensively assess the full range of side effects (weight gain, sexual dysfunction, aversive subjective experiences, etc.), other than movement disorders, that are recognised as occurring with first- and/or second-generation antipsychotics. For this study, an enhanced version of the ANNSERS was generated (ANNSERS-E) by adding potential cardiac symptoms such as palpitations, dizziness and syncope.

Metabolic side effects were assessed at baseline, and at the 12-week follow-up only, using an obesity measure [body mass index (BMI) and waist circumference] and assessment of blood pressure, serum prolactin concentration, plasma glucose concentration (non-fasting sample) and lipid profile. In line with best practice safety monitoring,⁵⁴ an electrocardiogram (ECG) was done and reported on at baseline, before the study medication was initiated, to establish a baseline for any subsequent cardiac monitoring and exclude cardiac contraindications to potentially high-dose antipsychotic medication, including long QT syndromes.

With regard to EPSs, drug-induced parkinsonism was assessed using the Simpson and Angus⁵⁵ Extrapyramidal Side Effects Scale (EPSE).⁵⁶ The Barnes Akathisia Rating Scale (BARS)⁵⁷ was used to assess akathisia, and the Abnormal Involuntary Movement Scale (AIMS)^{58,59} for rating tardive dyskinesia. Researchers received thorough training on the use of these scales.

Health economics measures

The costs and health benefits for a cost-effectiveness acceptability and net benefit analysis were also measured. The primary economic measure was the incremental cost-effectiveness ratio (ICER) of clozapine augmentation with amisulpride, estimated as net cost of such clozapine augmentation divided by net QALY of clozapine augmentation.

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 sections *The addition of study sites* to *Changes to study medication procedures*.

The addition of study sites

Additional sites were added as the trial progressed and, in total, took the number of study sites from 4 to 23.

The addition of screening electrocardiography

Electrocardiography to exclude cardiac contraindications and establish a baseline for any subsequent cardiac monitoring was added to the protocol prior to randomisation of the first participant.

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.

Changes to study medication procedures

Several changes were made to allow clinicians and site pharmacies more flexibility to manage the study medication. The option of repackaging trial medication into dose administration boxes (1 week at a time) was introduced, and a standardised approach to the management of temperature excursions in pharmacies was added for recorded temperatures between 25 °C and 30 °C. Moreover, the addition of an option for the prescriber to provide a further 28-day supply of study medication after the final 12-week follow-up assessment was added. In combination with the direct unblinding of the referring psychiatrist, this allowed time for participants allocated to the amisulpride arm of the trial to be provided with a standard prescription of amisulpride and, therefore, allowed an uninterrupted supply of medication when the participant and prescribing clinician agreed that this was desirable.

Patient and public involvement

A service user group contributed to the design of the study at the proposal stage. In particular, feedback from qualitative interviews with service users highlighted the relevance of a systematic assessment of side effects, including subjective experience. Once funded, two experts by experience, were involved in the trial throughout: one a service user and the other a parent and carer of a service user. These individuals sat on the Trial Steering Committee and the Trial Management Group, respectively, and, as a result, contributed to both trial oversight and the strategic direction of the trial, including ways to improve the recruitment rate.

Both of the experts by experience who were members of the trial's oversight committees made additional contributions. These included shaping the content of the website and newsletters, and communicating the importance of the study to health-care professionals through the Clinical Research Network. The last, in particular, was well received and influenced clinician engagement in the trial.

One further issue that was felt to particularly necessitate the perspective of service users was whether or not to introduce remuneration for completing assessments, and we sought the opinion of a wider network of service users through support from the Clinical Research Network on this issue before making a decision.

Participants

People aged 18–65 years with schizophrenia that had proved to be unresponsive, at a criterion level of persistent symptom severity (as used by Honer *et al.*³⁰) and impaired social function, to an adequate trial of clozapine monotherapy in terms of dosage, duration and adherence, and who were competent and willing to provide written, informed consent.

Inclusion criteria

To be eligible for enrolment, a patient's illness had to meet a criterion level of persistent symptom severity (as used by Honer *et al.*³⁰) and the patient had to exhibit impaired social function, despite an adequate trial of clozapine monotherapy in terms of dosage, duration and adherence:

- treatment for at least 12 weeks at a stable dose of 400 mg or more per day of clozapine, unless the size of the dose was limited by side effects
- a total score of ≥ 80 at baseline on the PANSS;^{45,46} the range of possible scores is 30–210, with higher scores indicating more severe symptoms
- a clinical global impression (CGI)⁵⁸ score of ≥ 4 (range of possible scores 1 = not mentally ill to 7 = extremely ill)
- a SOFAS⁴⁹ score of ≤ 40 ; range of possible scores 1–100, with lower scores indicating impaired functioning
- clinically stable for the last 3 months, with a consistent clozapine regimen.

Exclusion criteria

- Clinically significant alcohol/substance use in the previous 3 months.
- The presence of a developmental disability.
- Indication for current treatment with clozapine was intolerance or movement disorder rather than a treatment-refractory schizophrenic illness.
- A previous trial of clozapine augmentation with amisulpride.
- Existing relevant physical health problems such as cardiovascular disease, previous problems with prolactin levels or impaired liver/renal function.
- Any woman who was pregnant or planning a pregnancy, and any woman of child-bearing potential unless using adequate contraception.

Pharmacological intervention

The pharmacological intervention was the augmentation of clozapine treatment with another second-generation antipsychotic, amisulpride, or placebo: 400 mg of amisulpride or two placebo capsules for the first 4 weeks, with the option of titrating up to 800 mg of amisulpride or four placebo capsules for the remaining 8 weeks. The amisulpride and placebo tablets were encapsulated to look identical. A fully automated online (and telephone) randomisation service was provided by the Clinical Trials Research Unit, University of Sheffield, Sheffield, UK. In addition, a 24-hour unblinding service was provided by Emergency Scientific and Medical Services (ESMS Global; Medical Toxicology Information Service Ltd, London, UK).

Data analysis

Clinical data analysis

All the main analyses were performed on an intention-to-treat basis. Baseline summary statistics by randomised group were calculated. Group differences in the primary outcome (criterion response threshold of > 20% reduction in total PANSS score) and other binary outcome measures were evaluated through the use of logistic regression after allowing for stratification by baseline symptom severity. Differences in quantitative outcome measures were evaluated through corresponding analysis of covariance model, controlling for baseline symptom severity (the stratification variable) and baseline values of the outcome in question. The results of the trial are presented following the standard Consolidated Standards of Reporting Trials (CONSORT) recommendations.

There were three interim analyses carried out by the trial statistician for the Data Monitoring and Ethics Committee (DMEC) for the first three meetings. Baseline sex, age and PANSS score, by randomised group, were shown to check for imbalances between randomised groups. Analyses were limited to the primary outcome and adverse events. However, as fewer participants than projected had been recruited and completed the 12-week follow-up at these time points, it was not possible to analyse data in a similar way to the final analysis. For the second and third meetings, Fisher's exact tests and chi-squared tests were carried out to assess randomised group comparisons. There were alpha spending plans in place for efficacy (> 20% reduction in PANSS score) and safety (adverse events). However, all interim analyses showed *p*-values greater than those set in the alpha spending plan. At subsequent meetings, overall statistics were presented (i.e. without disclosure of treatment allocation). Additionally, as the final study population was much smaller than the sample size calculation (approximately one-third recruited), it was decided to revert to the conventional threshold of $p < 0.05$ to signify statistical significance. With the data available, to show a significant difference between randomised groups would have required a very large difference in outcome, so it would have been futile setting the *p*-value lower than the conventional *p*-value (as would have been the case if we had used the final *p*-value from the alpha spending plan).

Given the tentative evidence in the published literature, suggesting that a significant clinical response to the amisulpride intervention being assessed may not be evident before 10 weeks of treatment, the 6-week data were used to determine whether or not there was earlier benefit from the intervention. The 6-week outcome data were also examined as a (tertiary) outcome, looking at the data longitudinally using mixed-effects modelling using both 6- and 12-week outcomes and controlling for baseline values of the given measure. Mixed-effects modelling does not assume that outcome data are independent of one another (in this case, outcome values at 6 weeks are related to outcome values at 12 weeks), as standard methods such as multiple linear regression do. If methods that assume independence were used with longitudinal data, then it is likely the standard errors would be too small, giving 95% CIs that were too narrow. This mixed-effects modelling included a dichotomous time variable indicating the time point (6 or 12 weeks) and a variable indicating randomised group. It was possible to undertake this analysis only on outcomes that were measured at all three time points (baseline, 6 weeks and 12 weeks); however, it is possible to include those participants in whom data from only one of the two follow-up time points were available. There was a random intercept for each participant.

Per-protocol sensitivity analyses were also conducted. Those participants taking mood stabilisers, antidepressants or antipsychotic medication (other than the randomised medication and clozapine) at either 6 or 12 weeks were excluded. Analyses were then carried out using the same methods as the primary analyses, although unadjusted (that is not adjusting for baseline symptom severity or baseline values of the outcome in question) because of the large decrease in power as a result of the large numbers of participants taking one of these classes of medication (small numbers who were only taking the study medications) as a result of the stricter inclusion criteria. Predictors of missingness of the primary outcome were assessed using means (SDs), medians [interquartile ranges (IQRs)] or frequencies (%) depending on the distribution of the data. However, statistical tests were not carried out as only a small absolute number of participants had missing values for the primary outcome. It was decided, a priori, that imputation methods would not be used (i.e. complete-case analysis was used).

Data were analysed using Stata version 13.0 for Windows (StataCorp, College Station, TX, USA).

Health economic analysis

Approach

The framework for the within-trial and economic model analyses was cost-effectiveness analysis, to estimate the net cost per unit of health benefit gained by amisulpride augmentation. A cost-effectiveness acceptability approach was used to estimate the likelihood that amisulpride augmentation is cost-effective.

The population for the economic evaluation (within trial and economic model) consists of people who are unresponsive to clozapine, require additional treatment and have no contraindications for amisulpride augmentation. The intervention is clozapine augmented by amisulpride compared with clozapine not augmented by amisulpride.

The measure of health benefit for the analyses is the QALY. The primary outcome measure for all the economic analyses is the ICER (e.g. cost per QALY gained). The time horizon for the within-trial analyses is the 12 weeks from entry into the trial (baseline) to the final scheduled follow-up assessment. The time horizon for the economic model is 1–10 years from initiating clozapine augmented by amisulpride. The perspective for all the economic analyses is the health- and social-care sector (that incur the costs of providing care) and the patient (for health benefits). Previous evaluations of clozapine related treatment suggest that this approximates a broadly societal perspective.^{60,61}

The within-trial analysis used an intent-to-treat approach and included all eligible participants randomised to start treatment in both trial groups.

Within-trial analyses

Direct costs

The range of costs included the costs of the following formal health and social care services:

1. inpatient psychiatric and non-psychiatric care (including intensive care, emergency and crisis admissions)
2. hospital outpatient and day hospital attendances
3. primary care contacts with the general practitioner (GP) and GP practice staff (including office and home visits)
4. medicines taken on a daily basis
5. community mental health-care contacts
6. social care contacts.

Most of the resource-use data were collected using an economic patient questionnaire (EPQ) for each patient to identify the services used. Participants who reported using hospital inpatient and outpatient services were asked for details of the hospitals they attended. Data on the number of admissions, length of stay, number of outpatient visits were collected from case records at each of the hospitals reported by the participants. The frequency of other service use was collected from each patient using the EPQ. The data on service use were collected at the baseline and 12-week assessments. Data on medicines (dose, frequency, duration) were collected at baseline and at 6 weeks and 12 weeks.

The direct costs were estimated from resource-use data combined with the most recent published national unit costs available at the time of data analysis. These were the Department of Health's *National Schedules of Reference Costs 2013–2014*,⁶² the *Unit Costs of Health and Social Care 2014* produced by the Personal Social Services Research Unit, University of Kent⁶³ and the *British National Formulary*⁶⁴ for the price year 2013–14. Each item of service use was costed by multiplying the quantity of service used with the average unit cost for that item.

The cost of amisulpride augmentation was estimated from the drug accountability records collected as part of the trial. This recorded the number of 400-mg capsules per day that were prescribed at baseline, at week 4 and at week 8 and whether or not the medication was received by the participant.

Quality-adjusted life-years

Quality-adjusted life-years gained from baseline to end of the scheduled 12-week follow-up were estimated as the number of weeks multiplied by the utility of observed survival. The utility values were estimated from the EuroQol EQ-5D health status questionnaire and the associated published societal utility tariffs. The EQ-5D three levels (EQ-5D-3L) version was used in the trial (no problems, some problems, severe problems/unable to do activity) and was included in the baseline and 12-week follow-up assessment interviews conducted with all the trial participants.

The EQ-5D is a generic and validated health status questionnaire shown to have acceptable validity in people with schizophrenia in European countries.^{59,65,66} The EQ-5D has been used successfully in two recent UK trials of antipsychotics in schizophrenia.^{60,67} Data from these trials demonstrated that the EQ-5D correlates with clinical quality of life and effectiveness measures, and is sensitive to change.

The EQ-5D-3L gives a profile of the individual's health state at the time of assessment. Each possible health state has a published utility weight. Using the published tariff for the UK,⁶⁸ the health profile for each individual over the duration of follow-up was converted to a single utility value. QALYs were then estimated as:

$$\text{QALY} = \Sigma\{[(U_i + U_{i+1})/2] \times (t_{i+1} - t_i)\}, \quad (1)$$

where U_i = utility value and t_i = number of days between assessments for participant i .

Missing data

The primary outcome for the economic analysis combines a measure of cost and a measure of health benefit. This is in contrast to the analyses of the clinical outcomes, which is conducted for a single measure. One implication is that the impact of missing observations can be higher for the economic analyses than for the clinical analyses. From experience in previous clinical and economic trials, it was anticipated that there would be missing observations about use of services, for those people who completed the 12-week assessment.^{60,67} This can then lead to a low proportion of participants with complete cost and QALY data, which can increase bias and reduce the robustness of the economic analysis. Accordingly, we specified the use of multiple imputation for the economic data in the protocol and analysis plan.

There were complete EQ-5D data for all the people who completed a 12-week assessment. However, there were missing observations for the cost data. These were treated as missing at random. Multiple imputation was used to impute values for the different cost categories. Data were imputed for missing observations at both baseline and at the 12-week assessment. Total costs were generated from these imputed data (using the Stata passive estimate command).

The imputations were conducted in Stata version 13.1, using predictive mean matching and sequential chained equations. The predictive mean-matching models included demographic and clinical variables. These were initially selected from measures previously reported to be statistically and conceptually associated with costs and or QALYs. The selection of variables was further informed by correlation analyses of the pooled baseline data.⁶⁹

Economic analyses

Descriptive analysis was used to summarise the EQ-5D data, QALYs, service use and cost. Regression analysis was used to estimate incremental (net) costs and QALYs accounting for the impact of key covariates. The key covariates were identified from the literature and analyses used to identify variables for the multiple imputation models (described in *Missing data*).

The primary measure for the economic analysis was the ICER. Accordingly, no statistical tests of differences in mean costs or outcomes were conducted. The ICER was estimated as the net cost divided by the net QALY estimates from the regression analyses.

The estimates of net costs and outcomes from the regression were bootstrapped to simulate 10,000 pairs of net cost and net outcomes for the amisulpride-augmentation group. These simulated pairs of net cost and net outcomes were used to generate cost-effectiveness acceptability curves (CEACs), as recommended by NICE for health technology appraisals.⁷⁰

The simulated data were also used to estimate the probability that clozapine plus amisulpride augmentation is cost-effective compared with clozapine alone. This takes a Bayesian approach to estimating the likelihood that the intervention is cost-effective and avoids hypothesis testing and risk of a type 1 error.

The approach described above to estimate CEACs and probability that amisulpride augmentation is cost-effective revalues the health benefits gained by the intervention in monetary terms. However, in the UK there is no universally agreed monetary value for the types of health benefit measures (such as QALYs or criterion response) typically used in cost-effectiveness analyses. An approach used in health care is to ask the question: what is the maximum amount decision-makers are willing to pay to gain one unit of health benefit? Accordingly, the simulated net QALY values from the bootstrap simulation were revalued using a range of maximum willingness-to-pay values from £1 to £30,000 to gain one QALY. This was based on the range of willingness-to-pay value thresholds (WTPTs) historically implied by NICE decisions.⁷¹

The data for the CEAC were derived by first revaluing each of the 10,000 net health benefit estimates from the bootstrap simulation by a single WTPT. This was repeated for each WTPT within the range used.

A net benefit (NB) statistic for each pair of simulated net costs and net outcomes for each WTPT can then be calculated. For example, if the measure of health benefit is the QALY, the NB of amisulpride augmentation is estimated as:

$$\text{NB} = (\text{net QALYs gained} \times \text{amount willing to pay to gain one QALY}) - \text{net cost.} \quad (2)$$

This calculation was repeated for each WTPT. The CEACs plotted the proportion of bootstrapped simulations where the net benefit of amisulpride augmentation is > 0 for each WTPT.^{72–75}

Sensitivity analysis

Sensitivity analyses were used to explore the impact of changing the methods used on the estimates of whether or not amisulpride augmentation was cost-effective. This included rerunning the analyses:

- for complete-case analysis rather than multiple imputation of missing observations
- using key measures of outcome for the clinical effectiveness analysis as the measure of health benefit to estimate the cost per person with a 20% criterion response gained and cost per person with no recorded adverse event gained
- excluding inpatient costs from the total cost (there was an imbalance in inpatient admissions at baseline and participants with inpatient admissions in the follow-up period were also inpatients at the baseline assessment)
- excluding medication costs from the total cost (there was a higher number of missing data for medication costs, which was also dominated by the cost of clozapine)
- for participants who did and did not have a 20% criterion response and for participants who did and did not have an adverse event recorded.

Economic model

The economic within-trial sensitivity analyses explored aspects of the trial design and participants that could affect generalisability. A key issue for the within-trial economic evaluation is the short length of follow-up and whether or not any savings in health-care costs or gains in QALYs may be sustained over a longer 12-month period.

An economic model was constructed using the same target population, perspective, health benefit measure and costs as the within-trial analyses. The intervention arm of the model was defined as clozapine with amisulpride augmentation. The control arm of the model was defined as clozapine with placebo augmentation.

A focused literature search identified no full economic evaluations of amisulpride-augmentation treatment or any clozapine-augmentation treatment that could be used to inform the economic model design or provide data to estimate model parameters. The searches were conducted in September 2015 and were restricted to the previous 10 years (restricted because of relevance in terms of resource-use and health-care service changes, as well as modelling techniques). The databases searched were: NHS Economic Evaluation Database (NHS EED), the HTA database, EMBASE, MEDLINE, PsycINFO and EconLit. The search strategy included treatment terms, for example, 'clozapine unresponsive' and 'clozapine augmentation' and economic evaluation terms derived from the NHS EED search strategy. Two clinical effectiveness reviews were found in a search of The Cochrane Library for clozapine-augmented therapy.^{76,77} These reviews revealed that there were insufficient data about the long-term effects of any augmentation on clinical outcomes or side effects. The reviews included a few studies with a follow-up of up to 1 year, which showed that some patients take longer to respond (responding between 6 months and 1 year into treatment).

Given the paucity of evidence for long-term use of clozapine augmentation, as well as the complexities of the disease area, it was concluded that there is little to gain from building a full economic model. The evidence collected in this clinical and economic trial is the most robust evidence available to inform the model structure and economic parameter estimates. Accordingly, to explore what happens after the

12-week trial period, a partial model was constructed. The model explored the impact of varying the probabilities that participants would experience improvement in symptoms (as measured by the PANSS) and that participants would experience side effects. The analyses were based on the assumption that these probabilities are key drivers of costs and QALYs.

The economic model used a simple Markov structure to model the impact of symptom improvement and side effects over 12 months, split into four 3-month cycles (*Figure 1*). The initial cycle was assigned the probabilities, costs and QALYs for amisulpride and clozapine, to mirror the outcome of the trial. The subsequent cycles used pooled trial data to estimate the baseline values. For the initial cycle the mean costs/QALYs for clozapine were used. The net saving/QALYs gain from the primary analysis were applied to the clozapine values to estimate the mean costs and QALYs for the initial cycle of the amisulpride choice.

All data were entered into the model as distributions. Beta distributions were used for the probability data. Gamma distributions were used for the cost and QALY data. Monte Carlo simulation in TreeAge software (TreeAge Pro Health Care Module 2015, TreeAge Software Inc., Williamstown, MA, USA) (10,000 iterations) was used to estimate the net costs, QALYs and ICER of amisulpride augmentation. Probabilistic sensitivity analysis was used to estimate the likelihood that amisulpride augmentation was cost-effective compared with clozapine and placebo.

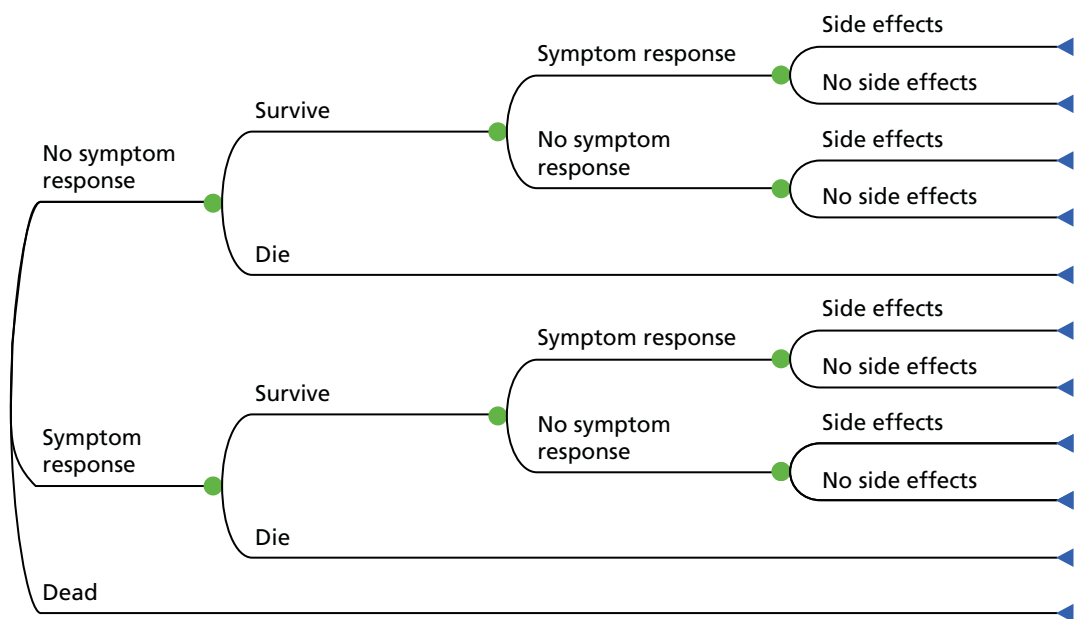


FIGURE 1 The Markov model.

Chapter 3 Results

Ninety-six patients were recruited and 68 patients were randomised, with 52 patients completing assigned treatment and assessment at the 12-week follow-up (Figure 2). This number of randomised participants fell well short of the target sample size. Table 1a shows that the participants in both groups were predominantly male and white. The mean age was close to 40 years in both groups. Almost all participants were not in paid work. Most had attended primary care services in the 3 months before baseline. Table 1b shows that, at baseline, the mean PANSS total score was a little higher in the placebo group than in the amisulpride group [98 (SD 24) and 93 (SD 13), respectively], although there were similar proportions with a high PANSS score (stratification variable). Mean PANSS negative symptom subscale scores were similar between the two groups, as were scores on other standardised instruments. Mean body weight, systolic and diastolic blood pressure were a little higher at baseline assessment in the amisulpride treatment group.

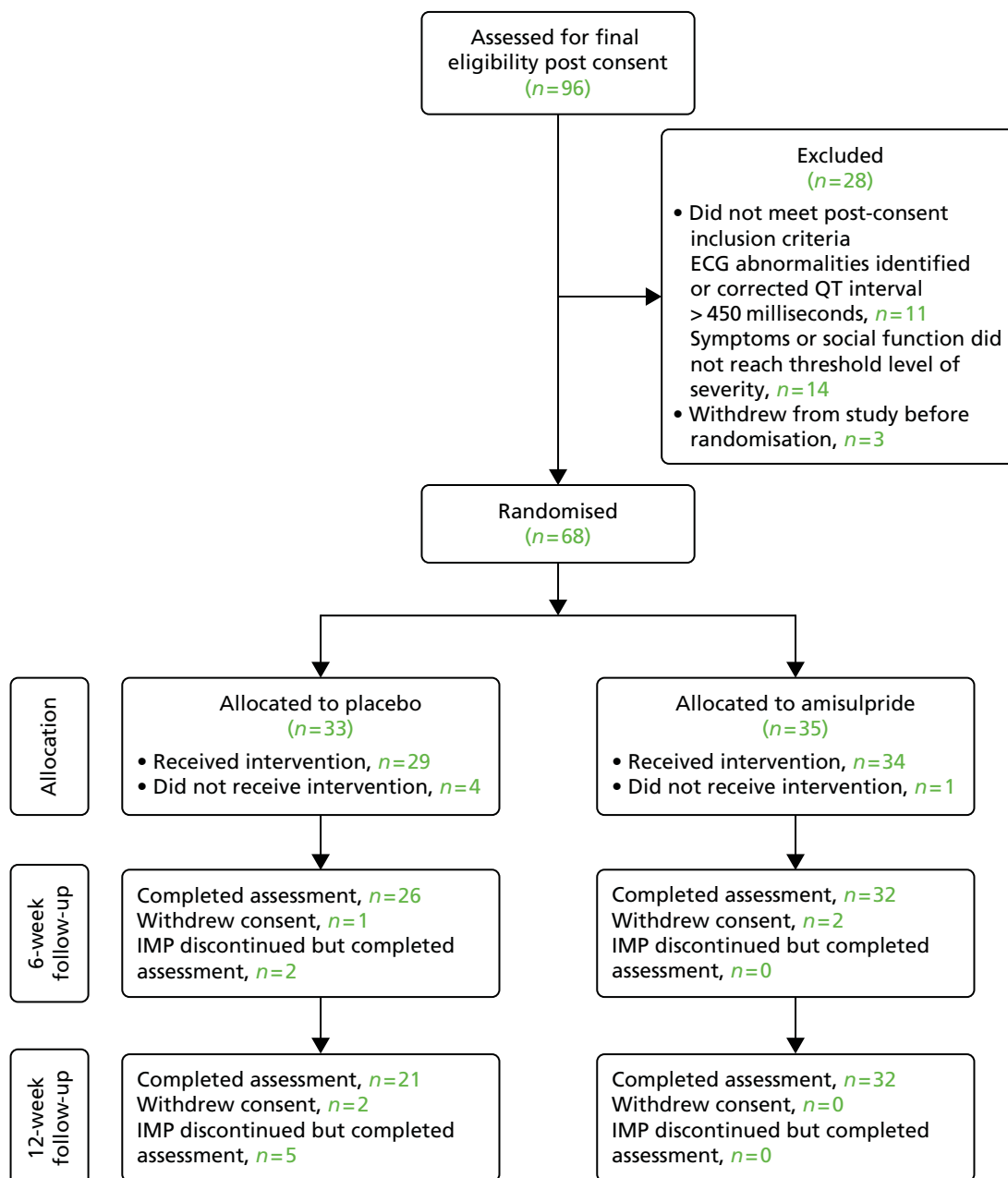


FIGURE 2 The CONSORT flow diagram. IMP, investigational medicinal product.

TABLE 1a Demographic characteristics and status of participants at baseline, by randomised groups

Variable	Treatment group			
	Amisulpride		Placebo	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Male	24/35	69	23/33	70
Age (years)	39	(11)	40	(10)
White	28/35	80	24/33	73
Living alone	12/32	38	11/28	39
Living with parents	5/32	16	8/28	29
Living with others	15/32	47	9/28	32
Owner occupied flat or house	0/34	0	0/29	0
Flat or house rented	19/34	56	21/29	72
Other accommodation	15/34	44	8/29	28
Not in paid employment because of treatment	24/25	96	23/25	92
Currently an inpatient	5/35	14	4/33	12
Psychiatric inpatient in the last 3 months	1/22	5	0/20	0
Non-psychiatric inpatient in the last 3 months	0/21	0	1/19	5
Any inpatient in the last 3 months	5/34	15	6/30	20
Psychiatric outpatient in the last 3 months	5/22	23	7/20	35
Non-psychiatric outpatient in the last 3 months	1/20	5	0/19	0
Any outpatient in the last 3 months	13/33	39	9/30	30
Psychiatric emergency in the last 3 months	0/21	0	0/20	0
Attended non-psychiatric A&E department in the last 3 months	0/21	0	0/19	0
Community-based services used in the last 3 months	14/33	42	16/29	55
Attended NHS day hospital or day centre in the last 3 months	0/22	0	1/20	5
Other primary or community care contacts in the last 3 months	28/33	85	26/29	90
In contact with the criminal justice system in the last 3 months	0/34	0	2/29	7

A&E, accident and emergency.

For each participant, up to three critical, target symptoms and/or behaviours refractory to treatment were identified at baseline by the responsible clinical team. Positive symptoms were most commonly identified: hallucinations were cited for 51% of the participants, delusions for 43% of the participants and suspiciousness/persecutory or paranoid ideas cited for 33% of the participants. Difficulty in abstract thinking or conceptual disorganisation were cited for 8% of the participants. With regard to negative symptoms, 20% of participants were considered to have a lack of drive, motivation, volition and/or spontaneity, whereas general negative symptoms were mentioned for 12% of the participants. Reduced social interaction was identified as a problem for 37% of the participants, and emotional withdrawal for 4% of the participants. Anxiety was relatively common, being identified as a persistent issue for 35% of the participants, whereas depression was a key symptom in only 9% of the participants. Lack of judgement or insight was named as an issue for 8% of the participants and poor attention for 4% of the participants. Poor management of physical health problems or self-care was named for 8% of the participants. One participant had particular difficulty with obsessive behaviour and one with hostility.

TABLE 1b Clinical characteristics of participants at baseline, by randomised groups

Variable	Treatment group			
	Amisulpride		Placebo	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Primary psychiatric diagnosis				
Schizophrenia	32/34	94	29/30	97
Schizophreniform disorder	1/34	3	0/30	0
Schizoaffective disorder	1/34	3	0/30	0
Psychosis NOS	0/34	0	1/30	3
Medication				
Any antidepressant	15/35	43	13/33	39
Any antipsychotic (excluding clozapine and amisulpride)	3/35	9	1/33	3
Any mood stabiliser	9/35	26	4/33	12
Cardiac symptoms, checked 7–10 days after starting study medication				
Irregular heartbeat	1/31	3	0/26	0
Shortness of breath	5/32	16	0/26	0
Dizziness	5/32	16	1/26	4
Fainting	0/31	0	0/26	0
Hypotension	0/30	0	0/26	0
Physical health measures				
Weight (kg)	96	(24)	91	(19)
Height (m)	1.72	(0.08)	1.73	(0.11)
BMI (kg/m ²)	33	(8)	30	(6)
Waist circumference (cm)	112	(13)	103	(13)
Systolic blood pressure (mmHg)	126	(17)	122	(11)
Diastolic blood pressure (mmHg)	83	(11)	82	(8)
Serum prolactin concentration (ng/ml), median (IQR)	12	(5–14)	12	(5–18)
Plasma glucose concentration (mmol/l), non-fasting sample	6.8	(2.7)	6.2	(2.9)
Total cholesterol concentration (mmol/l)	5.1	(1.3)	5.4	(1.2)
HDL cholesterol concentration (mmol/l)	1.1	(0.4)	1.4	(1.1)
LDL cholesterol concentration (mmol/l)	3.0	(1.4)	3.2	(0.9)
Triglyceride concentration (mmol/l), median (IQR)	2.0	(1.3–2.5)	1.7	(1.0–3.3)
Clinical assessment				
PANSS	93	(13)	98	(24)
PANSS high score (stratification variable)	16/35	46	14/33	42
PANSS negative symptom subscale score	25	(6)	25	(7)
CDSS, median (IQR)	5	(1–10)	5	(2–8)
SOFAS, median (IQR)	35	(32–39)	35	(30–40)
SES, median (IQR)	8	(4–13)	10	(4–18)
SAI, median (IQR)	12	(8–13)	12	(9–14)

continued

TABLE 1b Clinical characteristics of participants at baseline, by randomised groups (*continued*)

Variable	Treatment group			
	Amisulpride		Placebo	
	<i>n/N</i> or mean	% or (SD)	<i>n/N</i> or mean	% or (SD)
Side effects				
ANNSERS-E, median (IQR)	16	(11–22)	13	(10–24)
BARS, median (IQR)	0	(0–2)	2	(0–2)
Akathisia present (global clinical assessment score of ≥ 2)	3/33	9	4/31	13
AIMS positive: tardive dyskinesia	4/35	11	4/33	12
EPSE, median (IQR)	0.1	(0–0.3)	0.1	(0–0.3)
Parkinsonism present	10/29	34	6/24	25
HDL, high-density lipoprotein; LDL, low-density lipoprotein; NOS, not otherwise specified.				

Table 2 shows that, at the 6-week study assessment, the mean PANSS score was higher in the placebo group than in the amisulpride group [85 (SD 23) vs. 80 (SD 15)], although the proportion who showed a 20% drop in PANSS score from baseline was the same in both groups (25%). Median SES was lower in the placebo group [7 (IQR 4–14)] than in the amisulpride treatment group [10 (IQR 4–13)]. All other standardised scales show similar scores between treatment groups.

TABLE 2 Data at 6 weeks, by randomised groups

Variable	Treatment group			
	Amisulpride		Placebo	
	<i>n/N</i> or mean	% or (SD)	<i>n/N</i> or mean	% or (SD)
Clinical assessment				
PANSS	80	(15)	85	(23)
20% reduction in PANSS from baseline	8/32	25	7/28	25
PANSS negative symptom subscale	22	(8)	23	(7)
CDSS: depression, median (IQR)	4	(1–7)	3	(1–6)
SOFAS, median (IQR)	38	(35–40)	40	(35–41)
SES, median (IQR)	10	(4–13)	7	(4–14)
SAI, median (IQR)	12	(8–15)	12	(10–13)
Side effects				
ANNSERS-E, median (IQR)	13	(9–20)	15	(6–22)
BARS, median (IQR)	0	(0–2)	1	(0–2)
Akathisia present (global clinical assessment score of ≥ 2)	3/32	9	4/28	14
AIMS positive: tardive dyskinesia	1/32	3	1/28	4
EPSE, median (IQR)	0.2	(0.1–0.4)	0.1	(0.0–0.3)
Parkinsonism present	11/29	38	6/23	26
Medication				
Any antidepressant	11/32	34	13/28	46
Any antipsychotic (excluding clozapine and amisulpride)	4/32	13	1/28	4
Any mood stabiliser	7/32	22	5/28	18

Table 3a provides a comparison of the clinical characteristics and status of the amisulpride and placebo treatment groups at 12 weeks. Table 3b allows for comparison of primary and secondary outcomes at 12 weeks between the two treatment arms. The data show that the percentage of participants who showed a 20% reduction in PANSS score between baseline and 12 weeks was similar in both groups (44% of amisulpride participants and 40% of placebo participants). Mean weight, BMI, waist circumference and blood pressure were greater in the amisulpride group than in the placebo group. Median plasma prolactin concentration was higher in the amisulpride group than in the placebo group [43 ng/ml (IQR 9–87 ng/ml) vs. 11 ng/ml (IQR 7–12 ng/ml), respectively], as was mean plasma glucose concentration [6.9 mmol/l (SD 2.8 mmol/l) vs. 5.4 mmol/l (SD 0.7 mmol/l), respectively].

TABLE 3a Comparison of the clinical characteristics at 12 weeks, by randomised groups

Variable	Treatment group			
	Amisulpride		Placebo	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Living alone	12/31	39	11/25	44
Living with parents	5/31	16	5/25	20
Living with others	14/31	45	9/25	36
Owner occupied flat or house	0/32	0	0/25	0
Flat or house rented	18/32	56	17/25	68
Other accommodation	14/32	44	8/25	32
Not in paid employment because of treatment	22/25	88	19/20	95
Psychiatric inpatient in the last 3 months	3/22	14	0/14	0
Non-psychiatric inpatient in the last 3 months	1/22	5	0/15	0
Any inpatient in the last 3 months	5/32	16	3/25	12
Psychiatric outpatient in the last 3 months	5/19	26	3/14	21
Non-psychiatric outpatient in the last 3 months	2/19	11	1/14	7
Any outpatient in the last 3 months	12/32	38	6/32	24
Psychiatric emergency in the last 3 months	0/22	0	0/14	0
Attended A&E department in the last 3 months	0/22	0	0/15	0
Community-based services used in the last 3 months	10/30	33	14/25	56
Attended NHS day hospital or day centre in the last 3 months	0/21	0	0/14	0
Other primary or community care contacts in the last 3 months	23/32	72	19/25	76
In contact with the criminal justice system in the last 3 months	0/32	0	1/25	4
Medication				
Any antidepressant	11/32	34	12/25	48
Any antipsychotic (excluding clozapine and amisulpride)	2/32	6	2/25	8
Any mood stabiliser	6/32	19	5/25	20
Incomplete participation in the study	5/34	15	6/30	20
A&E, accident and emergency.				

TABLE 3b Comparison of primary and secondary outcomes at 12 weeks, by randomised groups

Variable	Treatment group			
	Amisulpride		Placebo	
	<i>n/N</i> or mean	% or (SD)	<i>n/N</i> or mean	% or (SD)
PANSS	76	(16)	80	(24)
Primary outcome				
20% reduction in total PANSS score from baseline	14/32	44	10/25	40
Secondary outcomes				
PANSS negative symptoms	21	(7)	21	(8)
SES, median (IQR)	8	(3–13)	7	(3–13)
CDSS, median (IQR)	5	(2–8)	3	(1–7)
SAI, median (IQR)	12	(10–13)	14	(9–15)
Physical health measures				
Weight (kg)	100	(25)	93	(22)
BMI (kg/m ²)	34	(9)	31	(7)
Waist circumference (cm)	112	(15)	103	(14)
Systolic blood pressure (mmHg)	124	(14)	119	(11)
Diastolic blood pressure (mmHg)	82	(10)	79	(6)
Serum prolactin concentration (ng/ml), median (IQR)	43	(9–87)	11	(7–12)
Plasma glucose concentration (mmol/l), non-fasting sample	6.9	(2.8)	5.4	(0.7)
Total cholesterol concentration (mmol/l)	5.1	(1.4)	4.7	(1.3)
HDL cholesterol concentration (mmol/l)	1.3	(0.6)	1.3	(0.5)
LDL cholesterol concentration (mmol/l)	2.8	(1.6)	2.9	(1.1)
Triglyceride concentration (mmol/l), median (IQR)	2.0	(1.3–3.8)	2.1	(1.2–2.9)
Side effects				
ANNSERS-E, median (IQR)	12	(7–22)	12	(9–15)
BARS, median (IQR)	1	(0–2)	1	(0–2)
Akathisia present (global clinical assessment score of ≥ 2)	2/32	6	4/25	16
AIMS positive: tardive dyskinesia	1/32	3	2/25	8
EPSE, median (IQR)	0.1	(0.0–0.4)	0.2	(0.0–0.5)
Parkinsonism present	8/28	29	7/18	39
HDL, high-density lipoprotein; LDL, low-density lipoprotein.				

Table 4 shows descriptive statistics about possible predictors of whether or not the primary outcome (20% reduction in PANSS score between baseline and 12-week follow-up) was missing ('missingness'). These may be of limited use because of the small numbers in the missing primary outcome group, some numbers being very small (with a maximum of 11).

TABLE 4 Baseline predictors of missingness of the primary outcome

Variable	Missingness of primary outcome			
	Present		Not present	
	n/N or median	% or (IQR)	n/N or median	% or (IQR)
Male	40/57	70	6/10	60
Age (years)	38	(31–46)	37	(31–42)
White	44/57	77	7/10	70
Living alone	21/54	39	2/6	33
Living with parents	12/54	22	1/6	17
Living with others	21/54	39	3/6	50
Flat or house rented	35/57	61	5/6	83
Other accommodation	22/57	39	1/6	17
Not in paid employment because of treatment	44/46	96	3/4	75
Currently an inpatient	9/57	16	0/10	0
Psychiatric inpatient in the last 3 months	1/38	3	0/4	0
Non-psychiatric inpatient in the last 3 months	0/36	0	1/4	25
Any inpatient in the last 3 months	10/57	18	1/7	14
Psychiatric outpatient in the last 3 months	11/38	29	1/4	25
Non-psychiatric outpatient in the last 3 months	1/35	3	0/4	0
Any outpatient in the last 3 months	19/56	34	3/7	43
Psychiatric emergency in the last 3 months	0/37	0	0/4	0
Attended A&E in the last 3 months	0/36	0	0/4	0
Community-based services used in the last 3 months	25/56	45	5/6	83
Attended NHS day hospital or day centre in the last 3 months	1/38	3	0/4	0
Other primary or community care contacts in the last 3 months	48/56	86	6/6	100
In contact with the criminal justice system in the last 3 months	2/57	4	0/6	0
Primary psychiatric diagnosis				
Schizophrenia	53/56	95	8/8	100
Schizophreniform disorder	1/56	2	0/8	0
Schizoaffective disorder	1/56	2	0/8	0
Psychosis NOS	1/56	2	0/8	0
Clinical assessment				
PANSS high score (stratification variable)	89	(84–98)	98	(86–111)
PANSS negative symptoms	25	(21–29)	28	(24–30)
CDSS depression	5	(1–10)	7	(4–14)
SOFAS	35	(31–40)	35	(30–39)
SES	9	(4–15)	9	(4–19)
SAI	12	(9–14)	13	(9–14)

continued

TABLE 4 Baseline predictors of missingness of the primary outcome (*continued*)

Variable	Missingness of primary outcome			
	Present		Not present	
	<i>n/N</i> or median	% or (IQR)	<i>n/N</i> or median	% or (IQR)
Side effects				
ANNSERS-E	15	(10–24)	20	(14–57)
BARS	0	(0–2)	3	(1–4)
Akathisia present (global clinical assessment score of ≥ 2)	4/56	7	3/8	38
AIMS positive: tardive dyskinesia	5/57	9	3/11	27
EPSE	0.1	(0.0–0.3)	0.0	(0.0–0.1)
Parkinsonism present	16/48	33	0/5	0
Other psychotropic medication				
Any antidepressant	25/57	43	3/11	27
Any antipsychotic (excluding clozapine and amisulpride)	4/57	7	0/11	0
Any mood stabiliser	11/57	19	2/11	18
Physical health measures				
Weight (kg)	89	(79–103)	84	(80–91)
Height (m)	1.72	(1.68–1.78)	1.70	(1.69–1.72)
BMI (kg/m ²)	30	(27–34)	29	(25–29)
Waist circumference (cm)	105	(100–115)	106	(96–106)
Systolic blood pressure (mmHg)	121	(115–133)	121	(112–129)
Diastolic blood pressure (mmHg)	80	(77–87)	83	(76–93)
Serum prolactin concentration (ng/ml)	12	(5–15)	11	(5–14)
Plasma glucose concentration (mmol/l), non-fasting sample	5.4	(5.0–6.6)	5.9	(4.0–8.3)
Total cholesterol concentration (mmol/l)	5.3	(4.5–6.1)	4.8	(4.0–5.5)
HDL cholesterol concentration (mmol/l)	1.1	(0.9–1.4)	1.7	(1.1–1.9)
LDL cholesterol concentration (mmol/l)	3.2	(2.5–3.7)	2.4	(2.1–3.1)
Triglycerides (mmol/l)	2.0	(1.4–3.2)	1.2	(0.9–1.5)
A&E, accident and emergency; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NOS, not otherwise specified.				

The data in *Table 5* show that the patients in the amisulpride group had higher odds than those assigned to placebo of achieving the primary outcome response criterion of a 20% reduction in PANSS total score at 12 weeks [OR 1.17 (95% CI 0.40 to 3.42)]. *Table 6* presents the unadjusted, per-protocol analysis in terms of the amisulpride intervention. This analysis excluded those participants who were prescribed an additional antipsychotic medication, a mood stabiliser or antidepressant at either 6 or 12 weeks, which was a substantial proportion. The findings are, therefore, hard to interpret: the estimates are close to zero and the 95% CIs are wide.

TABLE 5 Outcomes in terms of the amisulpride intervention

Variable	OR or coefficient	95% CI
Primary outcome		
20% reduction in PANSS from baseline	1.17 ^a	0.40 to 3.42
Secondary outcomes		
PANSS negative symptoms	-0.71	-3.22 to 1.81
SES	1.17	-1.63 to 3.97
CDSS	0.23	-1.54 to 2.00
SAI	0.02	-1.33 to 1.37
Side effects		
<i>Non-neurological</i>		
ANNSERS-E	1.58	-3.60 to 6.76
<i>Metabolic side effects</i>		
Weight (kg)	0.79	-1.40 to 2.99
BMI (kg/m ²)	-0.02	-1.05 to 1.01
Waist circumference (cm)	1.05	-2.33 to 4.42
Systolic blood pressure (mmHg)	3.49	-3.66 to 10.63
Diastolic blood pressure (mmHg)	3.33	-1.65 to 8.31
Serum prolactin concentration (ng/ml)	50.47	-8.86 to 109.80
Ln ^b serum prolactin concentration (ng/ml)	1.43	0.71 to 2.14
Plasma glucose concentration, non-fasting sample (mmol/l)	0.66	-0.22 to 1.54
Total cholesterol concentration (mmol/l)	0.48	-0.11 to 1.07
HDL cholesterol concentration (mmol/l)	0.09	-0.23 to 0.41
LDL cholesterol concentration (mmol/l)	0.11	-0.62 to 0.85
Triglycerides concentration (mmol/l)	0.78	-0.10 to 1.65
<i>Motor side effects</i>		
BARS	-0.23	-0.73 to 0.27
Akathisia present (global clinical assessment score of ≥ 2) ^c	0.35 ^a	0.06 to 2.09
AIMS positive ^c	0.37 ^a	0.03 to 4.34
EPSE	-0.04	-0.22 to 0.14
Extrapyramidal side effects present ^c	0.63 ^a	0.18 to 2.20
<p>^a Indicates result is an OR. ^b Logarithmic transformation. ^c Unadjusted result, too few events to do an adjusted analysis.</p>		

Table 7 presents the results of mixed-effects modelling to take time into account in terms of the amisulpride intervention. These reveal a time effect associated with a 20% reduction on the PANSS; the odds of 20% reduction on the PANSS at 12 weeks is 4.19 times that of a 20% reduction of 6 weeks (95% CI 1.20 to 14.56), controlling for baseline PANSS score and including the randomised condition (OR 1.43, 95% CI 0.24 to 8.44). Likewise, the PANSS negative subscale score shows that there is a slight decrease in score at 12 weeks compared with 6 weeks (coefficient -1.32, 95% CI -2.20 to -0.44), controlling for baseline negative PANSS score and including the randomised condition (coefficient -0.60, 95% CI -2.58 to 1.39).

TABLE 6 Unadjusted per-protocol analysis in terms of the amisulpride intervention

Variable	OR or coefficient	95% CI
Primary outcome		
20% reduction in PANSS from baseline	3.00 ^a	0.57 to 15.77
Secondary outcomes		
PANSS negative symptom subscale	-2.70	-9.53 to 4.13
SES: service engagement	-0.73	-6.44 to 4.97
CDSS: depression	0.06	-3.41 to 3.53
SAI: insight	1.07	-2.63 to 4.77
Physical health measures		
Weight (kg)	-1.86	-23.03 to 19.32
BMI (kg/m ²)	0.72	-5.79 to 7.23
Waist circumference (cm)	11.27	-3.60 to 26.14
Systolic blood pressure (mmHg)	0.81	-11.72 to 13.34
Diastolic blood pressure (mmHg)	2.23	-6.19 to 10.65
Serum prolactin concentration (ng/ml)	41.66	-57.26 to 140.59
Ln ^c serum prolactin concentration (ng/ml)	1.54	-0.13 to 3.20
Plasma glucose concentration: non-fasting sample (mmol/l)	0.72	-1.13 to 2.57
Total cholesterol concentration (mmol/l)	0.06	-1.42 to 1.53
HDL cholesterol concentration (mmol/l)	0.19	-0.19 to 0.57
LDL cholesterol concentration (mmol/l)	0.40	-1.35 to 2.16
Triglyceride concentration (mmol/l)	-0.56	-2.22 to 1.09
Side effects		
ANNSERS-E ^b	-1.25	-17.57 to 15.07
BARS	-0.27	-1.42 to 0.88
Akathisia present (global clinical assessment score of ≥ 2) ^d	-	-
AIMS positive: tardive dyskinesia ^d	-	-
EPSE	0.05	-0.21 to 0.32
Parkinsonism present	1.56 ^a	0.21 to 11.37

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

a Indicates result is an OR.

b Twelve participants in this analysis.

c Logarithmic transformation.

d Nobody in the amisulpride treatment group had akathisia or was AIMS positive.

Side effects

The data in *Table 7* regarding side effect assessment using the ANNSERS-E show that, over the course of the study, the mean ANNSERS-E total score was 3 points higher in those participants assigned to amisulpride than in those in the placebo group. The information in *Table 1b* shows a greater frequency of cardiac symptoms in the amisulpride group, when checked 7–10 days after starting study medication. The data in *Table 5* on plasma prolactin concentration (including following logarithmic transformation, i.e. ln prolactin) reveal that those participants in the amisulpride group had, on average, a much higher level during the study. Plasma prolactin concentration is 24% lower (95% CI 12% to 49%) in the placebo group than in the amisulpride group.

TABLE 7 Mixed-effects modelling to take time into account in terms of the amisulpride intervention

Variable	OR or coefficient	95% CI
Primary outcome		
20% reduction in PANSS from baseline	1.43 ^a	0.24 to 8.44
Secondary outcomes		
PANSS negative symptom subscale	-0.60	-2.58 to 1.39
SES	1.75	-0.54 to 4.04
CDSS: depression	0.19	-1.10 to 1.49
SAI	-0.52	-2.32 to 1.28
Side effects		
ANNSERS-E	3.11	-0.91 to 7.13
BARS	-0.11	-0.57 to 0.35
Akathisia present (global clinical assessment score of ≥ 2)	0.29 ^a	0.01 to 7.82
AIMS positive: tardive dyskinesia	0.18 ^a	0.00 to 32.67
EPSE	0.05	-0.09 to 0.19
Parkinsonism present ^b	-	-
<p>^a Indicates result is an OR. ^b Model did not converge.</p>		

Table 8 shows the data relating to the nature and frequency of adverse events reported during the trial. There were 65 adverse events in 31 participants; more of these events were in the amisulpride intervention group than in the placebo group (47 events vs. 18 events, respectively). Almost half of adverse events in the amisulpride group were in the cardiac, general or endocrine systems. With regard to the nature of the cardiac adverse events in the amisulpride-treated group, dizziness and breathlessness were the most common symptoms, each reported by six participants, with postural dizziness, irregular heartbeat and tachycardia each reported by two participants.

TABLE 8 Adverse events reported during the trial

	Treatment group			
	Amisulpride		Placebo	
	n/N	%	n/N	%
Adverse events as the denominator				
<i>Body system classification</i>				
Blood/bone marrow	1/47	2	1/18	6
Cardiac: general	12/47	26	1/18	6
Dermatological	1/47	2	3/18	17
Endocrine	10/47	21	0/18	0
Gastrointestinal	5/47	11	4/18	22
Infection	3/47	6	0/18	0
Metabolic/laboratory	2/47	4	0/18	0

continued

TABLE 8 Adverse events reported during the trial (*continued*)

	Treatment group			
	Amisulpride		Placebo	
	<i>n/N</i>	%	<i>n/N</i>	%
Neurology	1/47	2	1/18	6
Pain	1/47	2	0/18	0
Pulmonary/upper respiratory	4/47	9	0/18	0
Renal/genitourinary	0/47	0	1/18	6
Vascular	3/47	6	0/18	0
Other	4/47	9	7/18	39
Serious adverse event	1/45	2	2/18	11
<i>Adverse event severity</i>				
Mild	24/42	57	13/17	76
Moderate	15/42	36	2/17	12
Severe	3/42	7	2/17	12
Adverse event resulted in unblinding	1/44	2	2/18	11
<i>Trial drug related</i>				
Unrelated	17/47	36	1/18	6
Unlikely to be related	7/47	15	5/18	28
Possibly	7/47	15	10/18	56
Probably	13/47	28	2/18	11
Definitely	3/47	6	0/18	0
Adverse event unexpected	18/45	40	7/17	41
Outcome				
Resolved	24/44	55	12/14	86
Persisting	17/44	39	2/14	14
Not assessable	3/44	7	0/14	0
<i>Participants as the denominator</i>				
Any adverse event	21/35	60	10/33	30
Serious adverse event	1/35	3	2/33	6
Most severe adverse event				
None	14/35	40	23/32	72
Mild	9/35	26	5/32	16
Moderate	10/35	29	2/32	6
Severe	2/35	6	2/32	6
No adverse event	14/35	40	23/33	70
Adverse event not resulting in unblinding	20/35	57	8/33	24
Adverse event resulted in unblinding	1/35	3	2/33	6

Most of the adverse events reported were mild and resolved. Almost one-third of adverse events in the amisulpride group were either 'probably' or 'definitely' related to the study medication, compared with a little over one-tenth in the placebo group. Sixty per cent of participants in the amisulpride group had at least one adverse event, compared with 30% in the control group; however, serious adverse events were rare, with one person experiencing a serious adverse event in the amisulpride group and two people experiencing such an event in the placebo group.

Health economics

Within-trial analysis

Covariates for the analyses of cost and quality-adjusted life-years and imputation of missing data

The EQ-5D utility score at baseline was correlated with all the clinical measures except the SES and SOFAS (Pearson's correlation coefficient, $p \leq 0.05$; see *Appendix 1, Table 22*, for the Pearson correlation coefficients of each analysis). The following variables were selected as baseline covariates for the analyses to estimate net costs and QALYs. The covariates used in the analysis of QALYs were:

- PANSS
- whether or not the participant was white British
- whether or not the participant lived alone
- age
- baseline EQ-5D visual analogue scale (VAS) score.

The PANSS was included to take into account the relationship between utility and psychosis symptoms (Pearson's correlation coefficient = -0.304 ; $p = 0.014$). In addition, a complete set of baseline data for the PANSS measure was available, and correlated with the clinical measures that were associated with the EQ-5D utility score. Age was included to reflect the fact that health and, therefore, utility typically declines with age and was identified as an important covariate in previous studies of antipsychotic treatment.^{60,67} The binary variables to reflect whether or not the participants lived alone or were white British were included as proxies for social isolation. Additionally, whether or not a person is white British may act as a proxy for socioeconomic status, given that most of the trial participants were not in employment at the time of the trial.

The covariates used in the analysis of costs were:

- the costs in the 3 months prior to baseline
- study site
- whether or not the participant was white British
- whether or not the participant lived alone
- EQ-5D utility measure.

Past studies indicate that previous cost is a strong predictor of future cost.⁶⁰ Study site was included to reflect the fact that the total cost of treatment also depends on the availability and mix of services in different localities, particularly the relative provision of hospital compared with primary and community services. Whether or not a person lives alone or is white British may indicate a greater need for formal health and social services because of a lack of support, lower access to health, and socioeconomic deprivation. The EQ-5D was included as an overall measure of health and health need.

In addition to the baseline measures described in the preceding paragraph, to impute missing costs the clinical measures with complete data at baseline and follow-up, for participants who completed a follow-up assessment, were included in the imputation models. The variables with missing observations

that were imputed were inpatient, outpatient, community, primary care and medication costs and total costs for each assessment.

EQ-5D health status, utility and quality-adjusted life-years

There were no missing EQ-5D observations for participants who completed the 12-week follow-up assessment ($n = 57$). Tables 9 and 10 present the EQ-5D data for these participants. Baseline and follow-up data, where available, are reported in Appendix 1, Tables 20 and 21. Table 9 summarises the proportion of people with no problems on each of the EQ-5D health domains. Table 10 presents the mean VAS scores, which represent how participants rate their own health. Table 10 also includes the utility scores, estimated from the EQ-5D domains and published population weights. The utility scores are anchored at 0 (dead) and 1 (full health), with some states also valued as worse than death. There are no clear differences between the amisulpride and placebo groups at baseline or follow-up. As noted above, there were statistically significant correlations between the EQ-5D utility score and clinical measures of outcome, including measures of side effects. These indicated the utility score increased with decreased symptoms or

TABLE 9 EQ-5D scores and utility values at each assessment: participants with complete utility data

EQ-5D health states	Treatment group			
	Amisulpride ($n = 32/35$)		Placebo ($n = 25/33$)	
	<i>n/N</i>	%	<i>n/N</i>	%
Baseline				
No problem with mobility	25/32	78	18/25	72
No problem with self-care	27/32	84	19/25	76
No problem with usual activities	24/32	75	14/25	56
No problem with pain/discomfort	17/32	53	17/25	68
No problem with anxiety/depression	12/32	38	10/25	40
12-week assessment				
No problem with mobility	25/32	78	19/25	76
No problem with self-care	25/32	78	19/25	76
No problem with usual activities	23/32	72	13/25	52
No problem with pain/discomfort	18/32	56	16/25	64
No problem with anxiety/depression	11/32	34	11/25	44

TABLE 10 EQ-5D VAS scores and utility values at each assessment: participants with complete utility data

Assessment period	Treatment group			
	Amisulpride ($n = 32/35$)		Placebo ($n = 25/33$)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
EQ-5D VAS scores				
Baseline	58 (26)	52 to 56	59 (22)	53 to 66
12-week assessment	58 (23)	52 to 63	53 (23)	46 to 59
EQ-5D utility values				
Baseline	0.64 (0.37)	0.50 to 0.77	0.68 (0.38)	0.53 to 0.83
12-week assessment	0.64 (0.37)	0.51 to 0.77	0.65 (0.36)	0.50 to 0.79

lower levels of side effects. The results of the effectiveness analyses described above indicated that amisulpride may be associated with improvements in symptoms, but also increased side effect burden. This may explain the lack of difference in utility scores, which is a measure of overall health.

Table 11 summarises the QALY measure for participants who completed the 12-week follow-up assessment and for the sample of participants for whom complete cost and QALY data at baseline and follow-up were available. Again, there is no evidence of differences in QALYs between the two groups.

Service use and costs

Table 12 summarises the use of primary and community-based services and hospital-based services, for baseline and follow-up, for those participants with complete data about the services used at both baseline and follow-up.

TABLE 11 Quality-adjusted life-years: baseline to 12-week follow-up, unadjusted for baseline covariates

QALY	Treatment group					
	Amisulpride			Placebo		
	Sample size (n/N)	Mean (SD)	95% CI	Sample size (n/N)	Mean (SD)	95% CI
Participants for whom complete QALY and cost data at baseline and follow-up were available	18/35	0.178 (0.141)	0.127 to 0.228	15/33	0.188 (0.131)	0.141 to 0.235
Participants who completed the 12-week follow-up assessments	32/35	0.179 (0.106)	0.142 to 0.217	25/33	0.176 (0.108)	0.137 to 0.214

TABLE 12 Service use by participants with complete data at baseline and follow-up

Type of service	Treatment group	
	Amisulpride (n = 30)	Placebo (n = 22)
	Mean (SD)	Mean (SD)
Number of visits to community services in 3 months prior to baseline	3.20 (8.42)	7.64 (16.48)
Number of visits to community services baseline to follow-up	2.90 (8.05)	7.18 (15.62)
Number of GP visits in 3 months prior to baseline	0.93 (1.46)	1.59 (2.30)
Number of GP visits baseline to follow-up	0.67 (1.12)	1.23 (1.54)
Number of other primary visits in 3 months prior to baseline	5.57 (9.34)	4.64 (5.04)
Number of other primary visits baseline to follow-up	6.87 (9.66)	4.32 (6.99)
Total mental health outpatient visits in 3 months prior to baseline	0.27 (0.69)	1.82 (3.70)
Total mental health outpatient visits baseline to follow-up	0.63 (1.52)	1.05 (2.80)
Total physical health outpatient visits in 3 months prior to baseline	0.07 (0.25)	0.00 (0.00)
Total physical health outpatient visits baseline to follow-up	0.03 (0.18)	0.00 (0.00)
Length of stay for physical health admission to hospital in 3 months prior to baseline, days	0.00 (0.00)	0.00 (0.00)
Length of stay for physical health admission to hospital baseline to follow-up, days	0.03 (0.18)	0.00 (0.00)
Length of stay for mental health admission to hospital in 3 months prior to baseline, days	15.00 (34.11)	12.27 (31.61)
Length of stay for mental health admission to hospital baseline to follow-up, days	13.83 (36.24)	17.95 (39.14)

Table 13 reports the costs for the different types of services used. Overall, inpatient admissions for mental health care were the highest cost component, although a small proportion of participants had a mental health hospital admission (3 months to baseline – five participants in the amisulpride treatment group and three participants in the placebo group; baseline to follow-up – four participants in the amisulpride treatment group and five participants in the placebo group). Table 14 presents the total costs for participants with complete cost data, as well as the imputed cost for participants who completed the week 12 follow-up assessment. Overall, there are no clear differences in total cost between the amisulpride and placebo groups. The total costs are characterised by high levels of variance and overlap in the 95% CIs.

TABLE 13 Costs (£, 2014) of services used by participants with complete data at baseline and follow-up

Type of service	Treatment group	
	Amisulpride (n = 18), mean (SD)	Placebo (n = 15), mean (SD)
Cost of community services in 3 months prior to baseline	373 (552)	744 (2295)
Cost of community services baseline to follow-up	251 (436)	841 (2282)
Cost of primary care in 3 months prior to baseline	492 (654)	367 (436)
Cost of primary care baseline to follow-up	568 (839)	198 (274)
Cost of daily medications in 3 months prior to baseline	246 (142)	426 (716)
Cost of daily medications baseline to follow-up	309 (204)	232 (139)
Amisulpride baseline to follow-up	27 (5)	0 (0)
Cost of mental health outpatient visits in 3 months prior to baseline	53 (126)	278 (473)
Cost of mental health outpatient visits baseline to follow-up	166 (283)	191 (414)
Cost of physical health outpatient visits in 3 months prior to baseline	0 (0)	0 (0)
Cost of physical health outpatient visits baseline to follow-up	0 (0)	0 (0)
Cost of physical health admission to hospital in 3 months prior to baseline	6 (26)	0 (0)
Cost of physical health admission to hospital baseline to follow-up	0 (0)	0 (0)
Cost of mental health admission to hospital in 3 months prior to baseline	3690 (8490)	1476 (5717)
Cost of mental health admission to hospital baseline to follow-up	2193 (6460)	3378 (8916)

TABLE 14 Total costs (£, 2014) of health and social care

Total costs	Treatment group					
	Amisulpride			Placebo		
	Sample size (n/N)	Mean (SD)	95% CI	Sample size (n/N)	Mean (SD)	95% CI
Participants with complete cost data at baseline and follow-up						
3 months prior to baseline	18/35	4854 (10,844)	950 to 8759	15/33	3291 (8425)	258 to 6325
Baseline to 12-week follow-up assessment	18/35	3520 (8336)	519 to 6522	15/33	4840 (12,874)	205 to 9476
Participants who completed 12-week follow-up assessments: missing costs imputed						
3 months prior to baseline	32/35	5014 (9063)	1801 to 8226	25/33	4616 (8329)	1664 to 7568
Baseline to 12-week follow-up assessment	32/35	3988 (8103)	1116 to 6860	25/33	5330 (10,252)	1697 to 8964

Net costs, quality-adjusted life-years and cost-effectiveness of amisulpride augmentation

Table 15 reports the net costs and QALYs after adjusting for differences in baseline covariates. The data suggest a net saving for amisulpride and a small net gain in QALYs. It is important to note that the net cost and QALY data are associated with wide CIs that cross zero, which suggests that the differences are not statistically significant.

Figures 3 and 4 show the cost-effectiveness plane and CEAC. Table 16 reports the bootstrap simulations of net cost and QALYs, as well as the results of the cost-effectiveness acceptability analyses. These results show similar net costs and QALYs to the analysis adjusted for covariates. However, in this case, the 95th percentiles of cost indicate a net saving associated with augmentation of clozapine with amisulpride. The cost-effectiveness plane illustrates the scatter of the 10,000 simulated net costs, all of which indicate a net saving. Figure 3 also indicates the distribution of the 10,000 simulated net QALYs, which are evenly spread between net QALY gain and net QALY loss. Overall, there is a net saving with no clear difference in QALYs, with a mean net benefit of £1806 (SD £373, 95th percentiles £1088 to £2530). In this simulation, the probability that amisulpride augmentation is cost-effective is 1.

TABLE 15 Net costs (£, 2014) and QALYs of amisulpride augmentation, adjusted for baseline covariates

Analysis	Net cost		Net QALY	
	Mean (SE)	95% CI	Mean (SE)	95% CI
Participants who completed 12-week follow-up assessments: missing costs imputed	-£1788 (£1182)	-£4165 to £590	0.0009 (0.014)	-0.026 to 0.028

SE, standard error.

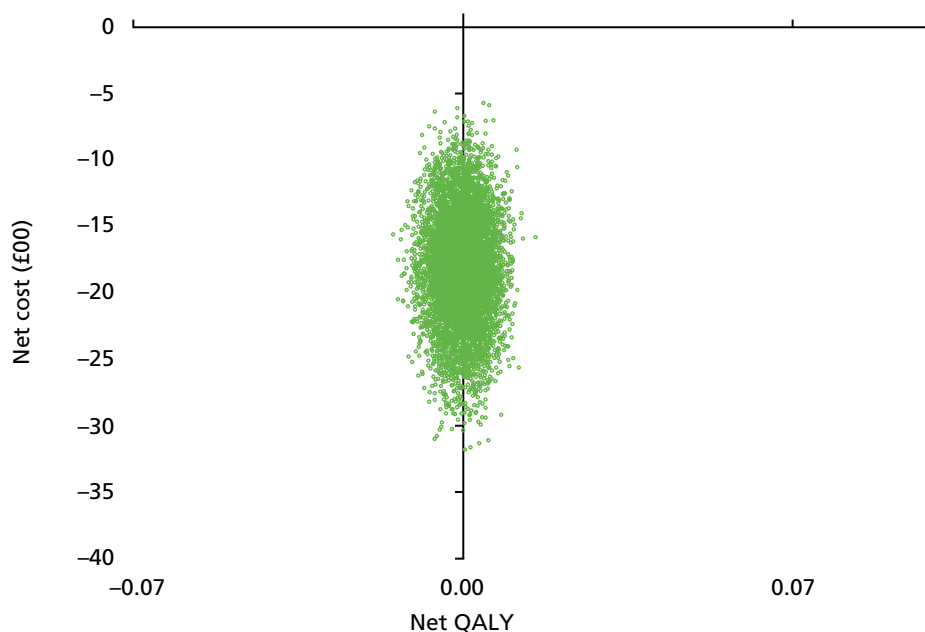


FIGURE 3 Cost-effectiveness plane of net costs and QALYs: primary analysis.

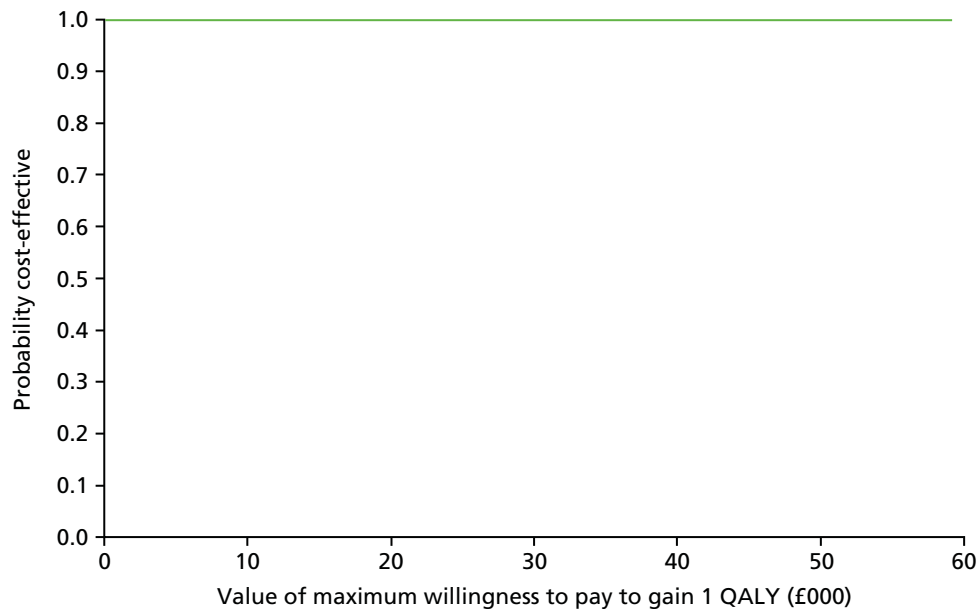


FIGURE 4 Cost-effectiveness acceptability curve, probability that amisulpride augmentation is cost-effective: primary analysis.

TABLE 16 Primary analysis of the cost-effectiveness of amisulpride augmentation: bootstrapped data

Statistic	Participants completing the 12-week follow-up assessments: missing costs imputed
Net (2014) cost (SE) [95th percentiles], £	-1816 (369) [-2540 to -1092]
Net QALY (SE) [95th percentiles]	0.0009 (0.004) [-0.007 to 0.008]
Incremental cost/QALY gained	Amisulpride dominates (net cost saving and no difference in QALYs)
Net benefit (SE) [95th percentiles], £; WTPT = £15,000	1806 (£373) [1088 to 2530]
Probability amisulpride cost-effective if WTPT = £15,000	1.00

SE, standard error.

Table 17 presents the results of the sensitivity analyses. Overall, these are similar to the results of the primary analysis, which supports a conclusion that amisulpride augmentation of clozapine is likely to be cost-effective. However, this conclusion only applies to the short treatment and follow-up period for the 57 participants who completed a follow-up assessment. In addition, excluding inpatient costs reduces the potential savings associated with amisulpride. If the configuration of available services is an important driver of whether or not a person can access and use inpatient care, the savings estimated in the primary analysis are likely to be overestimated.

Because amisulpride augmentation was associated with a higher rate of side effects and adverse events, there was no evidence that it was cost-effective when the cost per serious side effect (any severe non-neurological side effect, any EPS or any serious adverse event) was used as the measure of cost-effectiveness.

The economic model was used to explore the potential of amisulpride augmentation to be cost-effective over the longer time frame of 1 year. The results are discussed in the *Economic model* section below.

TABLE 17 Sensitivity analyses, adjusted for baseline covariates, bootstrapped data, within-trial analyses

Analysis	Net (2014) cost, £ (SE)	95th percentiles, £	Net QALY, (SE)	95th percentiles	Net (2014) benefit, £ (SD)	95th percentiles, £	Probability that amisulpride is cost-effective (WTPT = £15,000)
Sensitivity analyses							
Participants with complete cost data	-2011 (1761)	-5463 to 1441	-0.003 (0.027)	-0.057 to 0.050	1671 (1863)	-1016 to 5793	0.82
Excludes inpatient costs	-329 (132)	-587 to 71	0.0009 (0.004)	-0.007 to 0.008	327 (145)	52 to 629	0.99
Excludes costs of daily medications	-1864 (368)	-2586 to -1142	0.0009 (0.004)	-0.007 to 0.008	1855 (372)	1129 to 2575	1.00
Cost per person with a 20% response on the PANSS	-1816 (369)	-2540 to -1092	0.22 (0.19) people with a 20% response	0.155 to 0.586; people with a 20% response	3362 (2824); WTPT = £15,000 to gain one person with a response	-1842 to 882; WTPT = £15,000 to gain one person with a response	0.89
Cost per person with no serious side effects/adverse events	-1816 (369)	-2540 to -1092	-0.39 (0.28)	-0.94 to 0.16	-7563 (4058)	-15,422 to 522	0.04
SE, standard error.							

Economic model

Table 18 reports the baseline parameter values estimated from the trial data for cycles 2–4. The parameters were estimated from the pooled data for amisulpride augmentation and placebo. Regression of costs on whether or not a person had a 20% response on the PANSS, controlling for baseline total cost indicated a net saving associated with response. Regression of QALYs on whether or not a person had a 20% response on the PANSS, controlling for baseline total cost indicated a net increase in QALYs. Similarly, side effects were associated with an additional cost and a reduction in QALYs.

Table 19 shows the net costs and QALYs associated with amisulpride augmentation for the base-case analysis and sensitivity analyses, along with the probability that amisulpride is cost-effective. Overall, modelling the expected costs and QALYs over a 1-year time frame increased the variability in the results. This contributed to the reduction in the probability that amisulpride augmentation is cost-effective, from the values of 0.82–1.00 found in the within-trial analyses to between 0.54 and 0.58 for the model-based analyses. The model analyses were not sensitive to the probability of response, side effects or the time horizon used. This suggests that the initial net saving and QALY gain is not offset in the future if the probability of response and side effects for amisulpride is the same as clozapine from the second cycle onwards

TABLE 18 Baseline parameter values, cycles 2–4 of Markov model

Parameter	Mean (SD)	Distribution type	Source
Probability			
Probability of 20% response on the PANSS	0.40 (0.35)	Beta	Pooled AMICUS trial data
Probability of side effects	0.89 (0.22)	Beta	Pooled AMICUS trial data
Alive, point estimate (range)	0.99 (0.98–1)	Triangular	Healey <i>et al.</i> , 2012 ⁷⁸
Cost (£)			
Reduction in cost per person with 20% response on the PANSS	–2411 (6356)	Gamma	Pooled AMICUS trial data
Cost per person without 20% response on the PANSS	5904 (9218)	Gamma	Pooled AMICUS trial data
Additional cost per person with increased side effects ^a	757 (1293)	Gamma	Pooled AMICUS trial data
QALYs			
Additional QALY per person with 20% response on the PANSS	0.005 (0.111)	Gamma	Pooled AMICUS trial data
QALY per person without 20% response on the PANSS	0.174 (0.069)	Gamma	Pooled AMICUS trial data
Decrement in QALY per person with increased side effects ^b	–0.006 (0.011)	Gamma	Pooled AMICUS trial data

a There was no evidence that the number of people with one or more severe non-neurological side effects or EPSs resulted in an additional cost of health and social care services.

b There was no evidence that the number of people with one or more severe non-neurological side effects or extra-pyramidal side effects resulted in a loss of QALYs.

TABLE 19 Model analyses

Analysis	Net (2014) cost, £ (SE)	95th percentiles, £	Net QALY, (SE)	95th percentiles	Net (2014) benefit, £ (SD)	95th percentiles, £	Probability amisulpride is cost-effective (WTPT = £15,000)
Base-case analysis	-1935 (13,735)	-33,908 to 25,968	0.000 (0.153)	-0.309 to 0.309	1936 (13,882)	-24,201 to 37,041	0.58
Sensitivity analyses							
Probability of response differs between amisulpride ($p = 0.420$) and clozapine ($p = 0.37$) over all cycles	-2151 (14,174)	-34,853 to 26,542	0.009 (0.522)	-0.314 to 0.325	2682 (37,113)	-29,093 to 37,158	0.59
Probability of side effects differs between amisulpride ($p = 0.903$) and clozapine ($p = 0.885$) over all cycles	-1650 (13,755)	-32,483 to 27,595	0.003 (0.153)	-0.311 to 0.316	1813 (17,515)	-29,246 to 36,300	0.58
Probability of response and side effects differs between amisulpride ($p = 0.420$; $p = 0.903$) and clozapine ($p = 0.37$; $p = 0.885$) over all cycles	-1856 (14,329)	-34,330 to 27,110	-0.004 (0.588)	-0.326 to 0.314	1640 (18,162)	-32,499 to 39,282	0.58
Probability of response in cycles 2-4 differs between amisulpride ($p = 0$) and clozapine ($p = 0.4$)	-821 (14,274)	-32,264 to 29,410	-0.004 (0.203)	-0.320 to 0.305	582 (22,453)	-35,696 to 32,454	0.54
Time horizon: 10 years	-1749 (13,914)	-34,247 to 28,094	0.002 (0.153)	-0.313 to 0.315	1781 (13,925)	-25,265 to 34,292	0.58
SE, standard error.							

Chapter 4 Discussion

Efficacy

This trial is only the second double-blind, placebo-controlled RCT testing amisulpride augmentation of clozapine in patients with schizophrenia that has shown an insufficient response to clozapine treatment. It has a much larger sample size than the first RCT⁴³ but, nevertheless, it under-recruited, and the power of any analysis to detect significant differences between the active and placebo groups is necessarily limited. Looking at the primary outcome measure, the participants in the amisulpride group had higher odds of achieving the response criterion of a 20% or greater reduction in the total PANSS score by the end of the 12-week study, although this was not statistically significant. This advantage was not evident at 6 weeks, reinforcing the possibility that an adequate trial of clozapine augmentation with a second antipsychotic may be at least 10–12 weeks,¹⁸ that is, longer than the 4–6 weeks considered adequate for acute treatment of a psychotic episode. There was some evidence of a greater reduction in the PANSS negative subscale score by 12 weeks in those participants assigned to amisulpride than in those of the placebo group. This finding is in line with earlier reports of a greater improvement in negative symptoms than positive symptoms in randomised studies where clozapine augmentation with a second antipsychotic for treatment-refractory schizophrenia had proved to be beneficial,^{23,28} as well as some limited evidence for improvement in negative symptoms with amisulpride monotherapy.^{79–83}

The clinical relevance of a reduction in total PANSS score of 20% or more as a response threshold for people with treatment-refractory schizophrenia may have its limitations. First, it involves the interpretation of scores on a scale rarely used in clinical practice. Second, Leucht *et al.*⁸⁴ showed that even a 25% percentage reduction in the PANSS total score only reflected a reduction of the CGI scale score by one severity step. Thus, given the marked heterogeneity of the clinical presentation of treatment-refractory schizophrenia, future studies might consider adding an individualised response criterion, based on the change in severity of each participant's critical target symptoms. This last point is reinforced by the finding of a heterogeneous clinical picture in relation to the key symptoms and behaviours presenting in this study sample. Although persistent positive symptoms were the most common symptoms at baseline judged to be of clinical significance by the mental health professionals providing care, some participants presented other such target symptoms, including anxiety and negative symptoms in the avolition/amotivation domain.

Side effects

Amisulpride was chosen for this study because of the robust evidence for tolerability benefits, particularly a low risk of compounding characteristic clozapine side effects such as sedation, weight gain and other metabolic problems and a low risk of EPSs. Amisulpride is more likely than most second-generation antipsychotics to cause hyperprolactinaemia,⁸⁵ but causes little or no weight gain, has a similarly low risk of causing diabetes and lipid abnormalities and a relatively low liability for EPSs.^{86,87} With regard to cardiac side effects, QT interval prolongation and the potentially fatal arrhythmia, torsade de pointes, are not uncommon with overdose,⁸⁸ but the risk at therapeutic dosages is rather uncertain.^{89,90}

In our clinical trial, the results of the ANNSERS-E assessments revealed a greater side effect burden with amisulpride augmentation; that is, over time, the mean ANNSERS-E total score for those participants in the amisulpride-treated group was 3 points higher than that for the placebo group. However, the separate assessment of EPSs, such as akathisia and parkinsonism, revealed that these were not treatment-emergent problems with amisulpride augmentation of clozapine, despite previous studies reporting a high rate of tremor, bradykinesia and akathisia with this drug combination.^{43,76}

Among the participants in the amisulpride group, 60% experienced at least one adverse event over the course of the study, compared with 30% of participants in the placebo group. However, these adverse events were predominantly mild and the vast majority resolved. Serious adverse events were rare. Cardiac symptoms were a relatively common prompt for an adverse event report, occurring more commonly in the amisulpride group. Furthermore, an additional check for any emerging cardiac symptoms in the 7–10 days after starting study medication revealed that shortness of breath and dizziness were more common in the amisulpride treatment group. Amisulpride augmentation was also associated with endocrine effects; the most common was raised plasma prolactin concentration, an expected side effect that also provides some indirect but reassuring evidence of adherence to the study medication.

Mechanism of action

The rationale for the choice of an augmenting antipsychotic in patients on clozapine includes a complementary receptor profile, that is, potent D₂ dopamine receptor blockade.^{8,41,91} Amisulpride was chosen for this study because it fulfils this criterion in that it preferentially binds to dopamine D₂ and D₃ receptors in limbic rather than striatal brain structures^{92,93} and has low affinity for other dopamine receptor subtypes, although it also has affinity for a range of other receptors, including serotonergic, histaminergic and adrenergic receptors.

The limited benefit seen with amisulpride in this study supports the emerging notion that the rationale of potent D₂ blockade for an augmenting antipsychotic to treat clozapine-unresponsive illness may be simplistic. Treatment-refractory schizophrenia may have a more complex pathophysiology than illness showing a good therapeutic response to standard antipsychotic therapy; the underlying pathophysiology may even be non-dopaminergic. For example, dopamine synthesis capacity is lower in those patients with a treatment-resistant illness (indeed, no different from healthy controls) than in those with a responsive illness.^{94,95} Vayisoğlu and Anıl Yağcıoğlu⁹⁶ speculated that treatment-resistant illness may benefit from a multisite receptor effect rather than a stronger antidopaminergic effect.⁹⁷

Economic analyses

Overall, the economic analyses indicate that amisulpride augmentation has the potential to be cost-effective in the short term and, possibly, the longer term. The within-trial analysis indicated that amisulpride augmentation is associated with a net saving of £1816 (SD £369, 95th percentiles –£2540 to £1092) and no clear difference in QALYs. Although the extent of any savings is uncertain, because of the wide variation in costs, the cost-effectiveness acceptability analysis indicated that amisulpride augmentation can be cost-effective. The probability that amisulpride was cost-effective estimated from the bootstrap simulation was high with *p*-values of 0.82–1.00. An economic model extrapolated the results over a longer time frame of 1 year. This found similar net savings, but increased the variance associated with both net costs and QALYs. For the base case, the net saving was –£1935 (SD £13,735, 95th percentiles –£33,908 to £25,968). The 95th percentiles cross zero, indicating less certainty that there is a net saving for amisulpride augmentation; the probability that amisulpride is cost-effective is reduced to 0.54–0.58. However, the extent to which amisulpride augmentation represents value for money from the patients' perspective depends on their preferences and willingness to accept a potentially higher side effect burden for reduced symptoms.

Strengths and limitations of the health economics analyses

The within-trial economic evaluation was limited by the short 12-week follow-up period. This had several implications. First, the impact of service use at baseline, particularly inpatient stay may be relatively high compared with longer periods of follow-up. This was controlled for to some extent by including the costs for the 3 months prior to baseline as a covariate in the analyses of net cost. However, when combined with the small sample size, high level of variance and a high level of missing observations for service use data (*n* = 24/57 participants who completed a 12-week follow-up), the differences in costs may have been

driven by small but important differences in the use of high-cost, low-volume services. Excluding the costs of inpatient care from the analysis reduced the net saving associated with amisulpride from £1816 to £329. Even so, the probability that amisulpride was cost-effective was still high ($p = 0.99$).

The second consequence of the short follow-up period was that there was insufficient time to observe the impact of the increased side effects of amisulpride on the longer-term costs and QALYs. If the side effects were transient, then the net saving and QALY gains may be underestimated. Conversely, if the side effects were permanent and/or the rate of side effects increased, then the net saving and QALY gain would be overestimated. Additionally, the short follow-up period may not be sufficient to capture the impact of improved symptoms in the amisulpride group on service use and on overall health and QALYs. If the level of symptom improvement is constant over the longer term or increases, then the net savings and QALYs may be underestimated. The economic model analyses indicate that the within-trial results may be robust to large reductions in symptom response after the initial 12-week follow-up period. This applies when higher rates of side effects over the longer term are assigned to amisulpride.

As noted above, observations about service use were missing for a large proportion of participants. This was partly as a result of incomplete EPQ data and partly because of inconsistencies between the EPQ records and hospital case notes. Multiple imputation was used to impute missing costs for those participants who completed a 12-week follow-up assessment. It was assumed that the missing observations were missing at random. Analysis of the baseline pooled trial data indicated that it was possible to identify key covariates that were associated with costs, to use in the imputation model. Even so, the robustness of the multiple imputation model was reduced by the proportion of participants with missing observations (42%). Analysis of the smaller sample of participants with complete cost and QALY data indicated that the net saving associated with amisulpride treatment was less certain, and the probability that it was cost-effective reduced the p -value to 0.82.

For 11 out of 68 participants, no service use or EQ-5D data, at baseline or follow-up, were available. It was not possible to impute cost or QALY values for these participants. This, combined with the small sample and high rate of missing cost data, reduces confidence that the results are representative of all people with schizophrenia who are unresponsive to clozapine and eligible for amisulpride augmentation.

The EQ-5D utility values correlated well with the clinical measures of symptoms and side effects, indicating that it is a relevant measure of health benefit for this evaluation. Analysis of the pooled data for the economic model indicated that QALY values were higher for people who had a 20% response on the PANSS and lower for people who had one or more severe non-neurological or EPSs. This is an indication that, for the sample of participants in the trial, the measure reflects the impact of both side effects and symptom response. However, the QALY may not be an appropriate measure for complex needs or complex interventions.⁹⁸ People with schizophrenia have complex needs, with antipsychotic treatment adding therapy-induced side effects to the complexity of decision-making.^{99,100} In these situations the QALY may not adequately reflect the trade-off between side effects and symptom response for specific individuals requiring a change in treatment.

A focused literature search identified no full economic evaluations of amisulpride augmentation or any clozapine augmentation treatment that could be used to inform the economic model design or provide data to estimate model parameters. Two effectiveness reviews were found in a search of the Cochrane Library for clozapine augmentation.^{76,77} These reviews indicated there were insufficient data about the long-term effects of any augmentation on clinical outcomes or side effects. Given the paucity of evidence for long-term use of clozapine augmentation, as well as the complexities of the disease area, it was concluded that there is little to gain from building a full economic model. The evidence collected in this clinical and economic trial is the most robust evidence available to inform the model structure and economic parameter estimates. This meant that a partial model was used to explore the impact of varying the probabilities of symptom response and side effects. The analyses were based on the assumption that these probabilities are key drivers of cost and QALYs. These analyses indicated that amisulpride was

relatively robust to assumptions about the longer-term probability of response and side effects. However, the model was limited in scope, which reduces the generalisability and robustness of the results.

Implications of the findings of the health economics analyses

The results of the within-trial economic evaluation and economic model demonstrate there is uncertainty about the extent of savings as a result of amisulpride treatment over both the short and longer term. In addition, it is not clear whether or not the lack of evidence of differences in QALYs is because of a lack of effect or the small sample size and duration of this trial. Even so, the analyses do demonstrate that amisulpride augmentation is potentially cost-effective and that the analyses are relatively robust to different assumptions. These factors indicate a need for a longer-term, prospective evaluation of amisulpride augmentation. The costs of inpatient care over the short term were an important driver of costs. It is important that attention is paid to collecting accurate data about the number of admissions and the length of stay of admissions. The high level of missing observations indicates a need to test service-use data collection methods in each of the study centres prior to the start of the full trial.

It is acknowledged that trade-offs between positive and negative symptoms, side effects and functional outcomes are important issues in managing schizophrenia. However, there is a paucity of qualitative and quantitative research to understand the relative importance of these different aspects of treatment.^{99,100} Research that is codesigned with service users is required to explore the issues in more depth and to develop relevant quantitative surveys to measure and value preferences and priorities.

Recruitment

From early on, the AMICUS trial did not achieve the rate of recruitment that was anticipated and necessary in order to reach the original target of 230 participants. A rescue plan was agreed with the HTA programme, as funders, which included a lower recruitment target of 180 participants based on a reduced power of 80%. However, subsequently the recruitment rate decreased, partly as a result of loss of study momentum following a temporary closure of the study at the original end date. By the close of the extended recruitment period, we had achieved only 38% of the revised target. Negotiation of the hurdles of research governance, regulation, and NHS permissions, contracts and costs allocation meant that opening a single study site often took many months, undoubtedly impacting on our accrual. Nevertheless, even after sites were open to recruitment, referrals to the study were slow, despite feasibility work prior to this trial indicating that an adequate number of patients would fulfil the eligibility criteria.

The slow rate of participant recruitment was discussed by the Trial Management Group, during teleconferences with researchers at the study sites, and by the Trial Steering Committee. Particular consideration was given to barriers to recruitment and how these might be overcome. Some changes were made, such as the addition of a small remuneration for participants, following feedback that other clinical studies were offering this. Another amendment provided the option of an additional prescription of trial medication to allow time for unblinding at the end of the study follow-up period and, therefore, continuity of medication for the participant, an issue that had been raised by clinicians at sites.

Much of the discussion on the slow rate of recruitment revolved around the eligibility criteria and whether or not these were appropriate and pragmatic. Fifteen per cent of participants were excluded during final eligibility screening because their level of residual symptoms and/or impaired social function failed to reach the severity threshold necessary for inclusion. Given that these individuals had been identified by their clinical team as having shown a poor response to clozapine, we considered whether or not it would be pragmatic to include them in the trial. However, as the aim of the trial was to establish the risks and benefits of this augmentation strategy in patients with an indubitable treatment-refractory illness, we decided this was not appropriate. To modify these inclusion criteria would have resulted in a larger sample size and thus an increase in the power of the study, but it would have rendered any effectiveness findings more difficult to translate into recommendations for the management of treatment-refractory schizophrenia in clinical practice.

Another reason for the exclusion of participants was concern about ECG abnormalities or a prolonged corrected QT interval (> 450 milliseconds, following Medicines and Healthcare products Regulatory Agency guidance). Eleven per cent of participants were excluded on these criteria during final eligibility screening, but several further patients did not reach the consent stage as cardiac abnormalities had already been identified. We are aware that, subsequent to not being eligible to enter the trial, a number of these patients were prescribed amisulpride augmentation, raising the question of whether or not they should have been included in this trial as representative of routine clinical practice. However, the exclusion of patients with cardiac contraindications, including long QT syndromes, from exposure to potentially high-dose antipsychotic medication was in line with recommendations for best practice safety monitoring⁵⁴ and, therefore, it was not acceptable for this exclusion criterion to be removed, despite our awareness that the same conservative approach was not systematically adopted in clinical practice. The greater number of cardiac adverse events seen in participants in the amisulpride arm during the trial reassured us that we had made the right decision.

Feedback from researchers at the sites indicated that many clinical staff felt unable to review their case load and identify potential participants, citing competing clinical priorities, concerns about how introducing a trial to the patient might impact on their therapeutic relationship, or demonstrating a lack understanding of the clinical equipoise of the research question.^{101,102} On numerous occasions, clinicians expressed the view that it would be unethical for a patient to be given placebo rather than amisulpride. Furthermore, researchers found some clinical services commonly employed amisulpride augmentation as a pharmacological option for clozapine-refractory schizophrenia, limiting the number of eligible patients for the trial.

As referrals had to come from a member of a patient's clinical team, recruitment tended to occur in the services in which we encountered sympathetic clinical staff. Thus, many eligible patients in other areas missed the opportunity to participate. We opened additional trial sites over time in order to access more eligible patients, and worked hard to promote the trial with talks to clinical teams, newsletters, and researcher recruitment training days that covered engagement of both patients and clinical staff. However, recruitment failed to achieve the necessary rate for us to attain our target sample size. Indeed, 7 of the 23 sites failed to randomise a single participant.

Conclusions

The risk–benefit balance of amisulpride augmentation of clozapine for schizophrenia that has shown an insufficient response to a trial of clozapine monotherapy is worthy of further investigation in larger studies. This is the first study to provide detailed cost and QALY data about amisulpride augmentation of clozapine treatment. The economic analysis demonstrated that amisulpride augmentation has the potential to be cost-effective in the short term and, possibly, the longer term, but larger prospective RCTs of amisulpride augmentation that were methodologically sound and of adequate duration would be necessary to establish this. Whether or not such trials are feasible remains uncertain, given the continuing challenge of recruitment in mental health studies in the NHS. Nevertheless, this trial provides important process, clinical and economic data to inform the design of future studies.

The analysis of the data in our relatively small trial found that, even among patients with a clozapine-refractory illness, the addition of amisulpride was associated with a greater chance of improvement to a criterion level of overall symptom reduction within 12 weeks and some suggestion of improvement in negative symptoms. However, despite amisulpride being chosen for its favourable tolerability and safety profile, when combined with clozapine treatment in this study it was associated with a greater side effect burden, including cardiac side effects. This may partly reflect the thorough assessment of side effects in this study, which was more systematic and comprehensive than is generally conducted in clinical trials of antipsychotics.¹⁰³ These findings have implications for the nature and frequency of safety and tolerability monitoring of clozapine augmentation with a second antipsychotic in both clinical and research settings.

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South Staffordshire and Shropshire Healthcare NHS Foundation Trust (Dr Manoj Kumar).

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Tees, Esk and Wear Valley NHS Foundation Trust (Dr Raj Kumar).

West London Mental Health NHS Trust (Professor Thomas RE Barnes).

Study oversight committees

We thank all the members of the study oversight committees for their valued contributions.

Trial Steering Committee: Professor Stefan Priebe (independent chairperson), Professor Eileen Joyce, Ms Jenny Trite (expert by experience), Professor Tom Jamieson-Craig and Professor David Osborn.

DMEC: Professor Mohammed Abou-Saleh (chairperson), Dr Stuart Cox, Dr Louise Marston and Ms Ulrike Naumann.

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Verity C Leeson (Clinical Trials Manager, Centre for Mental Health, Imperial College London) 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, Oxleas NHS Foundation Trust) 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.

Louise Marston (Senior Trial Statistician, Department of Primary Care and Population Health and PRIMENT Clinical Trials Unit, University College) cowrote the original grant application, and the development and subsequent amendments of the trial protocol. She led the statistical analysis, and contributed to the interpretation and write-up of the results for the final report.

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Data sharing statement

All data are available on request from the corresponding author.

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Appendix 1 EQ-5D health status and utility

TABLE 20 EQ-5D scores and utility values at each assessment, participants with available utility data

EQ-5D health states	Treatment group	
	Amisulpride (n = 35)	Placebo (n = 33)
	n/N (%)	n/N (%)
Baseline		
No problem with mobility	26/34 (77)	14/31 (77)
No problem with self-care	29/34 (85)	23/31 (74)
No problem with usual activities	25/34 (74)	16/31 (52)
No problem with pain/discomfort	18/34 (53)	21/31 (68)
No problem with anxiety/depression	12/34 (35)	10/31 (32)
12-week assessment		
No problem with mobility	25/32 (78)	19/25 (76)
No problem with self-care	25/32 (78)	19/25 (76)
No problem with usual activities	23/32 (72)	13/25 (52)
No problem with pain/discomfort	18/32 (56)	16/25 (64)
No problem with anxiety/depression	12/32 (34)	10/25 (44)

TABLE 21 EQ-5D scores and utility values at each assessment, participants with available utility data

Assessment	Treatment group					
	Amisulpride			Placebo		
	Sample size (n/N)	Mean (SD)	95% CI	Sample size (n/N)	Mean (SD)	95% CI
EQ-5D VAS scores						
Baseline	34/35	58 (25)	49 to 67	31/33	57 (22)	49 to 65
12-week assessment	32/35	58 (23)	50 to 66	25/35	53 (23)	44 to 62
EQ-5D utility values						
Baseline	34/35	0.64 (0.36)	0.52 to 0.76	31/33	0.64 (0.36)	0.51 to 0.77
12-week assessment	32/35	0.64 (0.37)	0.51 to 0.77	25/35	0.65 (0.36)	0.50 to 0.79

TABLE 22 Correlation between EQ-5D utility scores and clinical measures

Assessment	Correlation with baseline EQ-5D utility weight
BARS at baseline	
Pearson's correlation	-0.292
<i>p</i> -value (two-tailed)	0.020*
<i>n</i>	63
Calgary at baseline	
Pearson's correlation	-0.655
<i>p</i> -value (two-tailed)	< 0.001**
<i>n</i>	64
PANSS at baseline	
Pearson's correlation	-0.304
<i>p</i> -value (two-tailed)	0.014*
<i>n</i>	65
SAI at baseline	
Pearson's correlation	-0.296
<i>p</i> -value (two-tailed)	0.017*
<i>n</i>	64
SES at baseline	
Pearson's correlation	-0.060
<i>p</i> -value (two-tailed)	0.641
<i>n</i>	62
SOFAS at baseline	
Pearson's correlation	0.028
<i>p</i> -value (two-tailed)	0.828
<i>n</i>	65
ANNSERS-E at baseline	
Pearson's correlation	-0.498
<i>p</i> -value (two-tailed)	0.001**
<i>n</i>	41
EPSE at baseline	
Pearson's correlation	-0.315
<i>p</i> -value (two-tailed)	0.021*
<i>n</i>	53
* <i>p</i> < 0.05; ** <i>p</i> < 0.01.	

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

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