

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

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Declared competing interests of authors: Thomas RE Barnes has received honoraria from Roche for speaking at educational meetings and has been a member of scientific advisory boards for Sunovion Pharmaceuticals Inc. and Otsuka Pharmaceutical Company Ltd/H. Lundbeck A/S in relation to antipsychotic medication. Carol Paton has undertaken consultancy work for Sunovion Pharmaceuticals Ltd and Eli Lilly and Company in relation to antipsychotic medication. Tom KJ Craig has received honoraria from Eli Lilly and Company and Sanofi for speaking at educational meetings. Patrick Keown has received an honorarium for speaking at an educational meeting and has been a member of a scientific advisory board for Otsuka Pharmaceutical Company Ltd/H. Lundbeck A/S in relation to antipsychotic medication, and has received support from Janssen Pharmaceutica to attend a conference. David Baldwin has received research funding from Pfizer Inc. and undertaken consultancy work for H. Lundbeck A/S. Glyn Lewis reports membership of Efficacy and Mechanism Evaluation board. Shôn Lewis reports a potential spin-out company, Clintouch.

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Scientific summary

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Background

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

Objective

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

Design

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

Setting

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

Participants

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

Interventions

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

Outcome measures

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

Results

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

Limitations

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

Conclusions

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

Future research

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

Trial registration

This trial is registered as ISRCTN42305247.

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