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

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Scientific summary

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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 D_2 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.

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