Amisulpride for very late-onset schizophrenia-like psychosis: the ATLAS three-arm RCT

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Scientific summary

The ATLAS three-arm RCT

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Scientific summary

Background

Very late-onset schizophrenia-like psychosis (VLOSLP) is a serious mental illness, characterised by the development of, usually, persecutory delusions, with or without hallucinations, in an individual who is aged > 60 years and who does not have dementia or a mood disorder. Patients with VLOSLP can experience symptoms for many years; their delusions cause distress and social withdrawal and may lead to conflict with family members and neighbours. Although antipsychotic drug treatment is sometimes prescribed, there have been no randomised controlled clinical trials to inform on efficacy and safety in this patient group. As older people are highly sensitive to the adverse effects of antipsychotics, clinicians may be reluctant to prescribe them for this group and this, combined with low levels of insight among patients, has meant that only about one-quarter of VLOSLP patients receive treatment. Most patients, consequently, are discharged from specialist mental health services, back to the care of their general practitioners, and their psychosis symptoms persist untreated.

Objectives

The Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis (ATLAS) trial was a parallel-group, double-blind, placebo-controlled, randomised clinical trial designed to address the following questions:

1. Is a low dose (i.e. 100 mg per day) of amisulpride superior to placebo in reducing psychosis symptoms over 12 weeks in patients with VLOSLP?
2. Are there any benefits associated with continuing treatment for a further 12 weeks compared with withdrawal to placebo?
3. Is 100 mg per day of amisulpride a safe and well-tolerated treatment for people with VLOSLP compared with placebo treatment?
4. What is the cost-effectiveness of amisulpride treatment over 12 weeks and of continuing treatment for a further 12 weeks compared with placebo treatment?

Methods

The ATLAS trial was a pragmatic, parallel-group, double-blind, placebo-controlled, randomised three-arm clinical trial with two stages. Stage 1 investigated the efficacy, tolerability and safety of 100 mg of oral amisulpride per day over 12 weeks compared with placebo. Stage 2 investigated the effects of amisulpride continuation versus withdrawal to placebo over a further 12 weeks.

Participants were patients with VLOSLP recruited from the community and inpatient services of specialist secondary care old age psychiatry services within 25 NHS mental health trusts in England and Scotland. Inclusion criteria were (1) diagnosis of VLOSLP according to International Consensus Group criteria and including onset of delusions and/or hallucinations after the age of 60 years, (2) Brief Psychiatric Rating Scale (BPRS) score of ≥ 30 points and (3) capacity to give informed consent for participation in the ATLAS trial. Exclusion criteria were (1) evidence of cognitive impairment or standardised Mini-Mental State Examination score of < 25 points, (2) diagnosis of affective disorder, (3) uncontrolled serious physical illness, (4) prescribed amisulpride in previous 28 days (patients treated with other antipsychotics in the previous 28 days but who still satisfied eligibility criteria and for whom stopping current antipsychotics was considered appropriate by their prescribing psychiatrist could participate) and (5) any contraindication to amisulpride.

Trial treatment was with overencapsulated 100 mg of amisulpride or placebo. Following informed consent and completion of baseline assessment, participants were randomly allocated to one of three groups: group A took 100 mg of amisulpride daily for 24 weeks, group B took 100 mg of amisulpride daily for 12 weeks followed by the placebo for 12 weeks and group C took the placebo for 12 weeks followed by 12 weeks of 100 mg of amisulpride daily.

There were two coprimary outcome measures: (1) change in psychosis symptoms assessed with the BPRS between baseline and week 12 and between week 12 and week 24 and (2) the proportion of patients withdrawing from trial treatment because of perceived lack of efficacy. Secondary outcomes included (1) extrapyramidal symptoms as measured with the Simpson–Angus Scale, (2) compliance measured by treatment discontinuation rates and the percentage of prescribed medication taken, (3) quality of life measured with the World Health Organization's quality-of-life scale and EuroQol-5 Dimensions (EQ-5D) and (4) cost-effectiveness calculated from the health and social care costs, unpaid carer costs and the EQ-5D.

Participants who received at least one dose of study treatment were included in intention-to-treat analyses using standard *t*-test and repeated measures regression methods.

Results

Out of 101 randomised participants, 92 took trial medication. Of the 92, 59 completed stage 1 treatment and 33 completed stage 2 treatment. Despite generally poor compliance, the improvement in BPRS at 12 weeks was 7.7 points [95% confidence interval (CI) 3.8 points to 11.5 points] greater with amisulpride than with placebo (11.7 vs. 4.2 points; $p = 0.0002$). In stage 2, scores improved by 1.1 point in participants who continued with amisulpride treatment but deteriorated by 5.2 points in those who were withdrawn to placebo, with a difference of 6.3 points (95% CI 0.9 points to 11.7 points; $p = 0.024$). Fewer participants who were allocated to the amisulpride group than the placebo group stopped treatment because of non-efficacy in stages 1 ($p = 0.01$) and 2 ($p = 0.031$). The number of participants stopping treatment because of extrapyramidal symptoms and other side effects did not differ significantly between amisulpride and placebo treatment.

There were no significant differences between the amisulpride and placebo groups on any of the secondary outcome measures in stages 1 or 2. Eleven per cent of patients allocated to the amisulpride group developed clinically significant extrapyramidal symptoms in stage 1 compared with 0% in the placebo-treated group ($p = 0.051$). In addition, serious adverse events were more common in the amisulpride group in stages 1 ($p = 0.057$) and 2 ($p = 0.19$) than in the placebo group.

In the health economic analyses, amisulpride treatment was associated with non-significant reductions in combined NHS, social care and unpaid carer support costs of £599 (95% CI –£1762 to £299) in stage 1 and £821 (95% CI –£1952 to £129) in stage 2; and non-significant reductions in quality-adjusted life-years in stage 1 (–0.009, 95% CI –0.042 to 0.024) and stage 2 (–0.19, 95% CI –0.076 to 0.049).

Conclusions

Low-dose amisulpride, at 100 mg per day, is an effective and well-tolerated treatment for patients with VLOSLP and benefits are maintained by prolonging treatment to 24 weeks. The improvements in psychosis symptoms that are seen with treatment should be balanced against the risks of side effects, particularly extrapyramidal symptoms, and ongoing safety monitoring is important.

Future research

Future research should examine ways of improving the engagement of patients with VLOSLP in treatment because their lack of insight into their illness or the potential for treatment to improve symptoms remains the most important factor limiting access to effective drug treatments.

Trial registration

This trial is registered as ISRCTN45593573 and EudraCT2010-022184-35.

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