Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID)

P Tyrer,1* P Oliver-Africano,1 R Romeo,2 M Knapp,2 S Dickens,1 N Bouras,3 Z Ahmed,4 S Cooray,5 S Deb,6 D Murphy,7 M Hare,4 M Meade,1 B Reece,1 K Kramo,1 S Bhaumik,8 D Harley,9 A Regan,10 D Thomas,11 B Rao,1 S Karatela,9 L Lenôtre,5 J Watson,8 A Soni,12 M Crawford,1 J Eliaahoo13 and B North13

1Department of Psychological Medicine, Imperial College, London, UK
2Centre for Economics of Mental Health, Box P024, Institute of Psychiatry, De Crespigny Park, London, UK
3Mental Health in Learning Disabilities Centre, King’s College London, Institute of Psychiatry, Estia Centre, Guy’s Hospital, London, UK
4Welsh Centre for Learning Disabilities Clinical Studies, University of Wales College of Medicine, Cardiff, UK
5Central North West London Foundation NHS Trust, Kingsbury Community Unit, Brent, London, UK
6Department of Psychiatry, University of Birmingham, Queen Elizabeth Psychiatric Hospital, Birmingham, UK
7Section of Brain Maturation, Institute of Psychiatry, London, UK
8Leicestershire Partnership NHS Trust, Leicester Frith Hospital, Leicester, UK
9Queensland Centre for Intellectual and Developmental Disability (QCIDD), School of Population Health, University of Queensland, Brisbane, Australia
10Harrow Primary Care NHS Trust, Orme Lodge, Stanmore, Middlesex, UK
11North East London Mental Health NHS Trust, Redbridge Learning Disability Service, Barkingside, Essex, UK
12West London Mental Health NHS Trust, Hammersmith & Fulham Mental Health Unit, London, UK
13Statistical Advisory Service, Imperial College, London, UK

*Corresponding author

Executive summary

Health Technology Assessment 2009; Vol. 13: No. 21
DOI: 10.3310/hta13210

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk
Executive summary: Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities

Background
Aggressive challenging behaviour is a common symptom in adults with intellectual disability and has many different causes, ranging from antisocial personality disorder to autism, mood disturbance and simple frustration over communication. Its course is variable and it is commonly treated with neuroleptic drugs. Haloperidol and chlorpromazine are licensed for this indication, but the evidence base for treatment with neuroleptic drugs is poor.

Objectives
• To compare the effects of treatment of aggressive challenging behaviour in adults with intellectual disability with haloperidol (a typical neuroleptic drug), risperidone (an atypical neuroleptic drug) and placebo in flexible dosage on episodes of aggression from 1 to 26 weeks.
• To compare the effects of haloperidol, risperidone and placebo after 4, 12 and 26 weeks in the short- and longer-term outcome of aggressive challenging behaviour in terms of quality of life, reduction in burden of carers and other behaviour disturbance.
• To assess the adverse effects of treatment of aggressive challenging behaviour in intellectual disability with haloperidol, risperidone and placebo.
• To compare the costs of care of treatment of aggressive challenging behaviour in intellectual disability with haloperidol, risperidone and placebo over a 6-month period.

Methods
The study design was a double-blind randomised controlled trial (RCT) of haloperidol, risperidone and placebo administered in flexible dosage (haloperidol 1.25–5.0 mg daily, risperidone 0.5–2.0 mg daily), with full, independent assessments of aggressive and aberrant behaviour, global improvement, carer burden, quality of life and adverse drug effects at baseline, 4, 12 and 26 weeks, accompanied by comparison of total costs of care of the three treatments in the 6 months before and after randomisation. At 12 weeks, patients were given the option of leaving the trial or continuing until 26 weeks. Assessments of overt aggression were also carried out with key workers at weekly intervals throughout the trial.

Participants
Patients were recruited from all those being treated by intellectual disability services in eight sites in England, one in Wales and one in Queensland, Australia. We included patients from all severity levels of intellectual disability, extended recruitment to include those who may have been treated with neuroleptic drugs in the past, and excluded only those who had previously been diagnosed as having a psychosis. A diagnosis of being within the group of autistic spectrum disorders was not an exclusion criterion, provided that psychosis was absent. However, those who had taken depot neuroleptics or any other form of injected neuroleptic medication treatment within the last 3 months, or continuous oral neuroleptic medication within the last week, were excluded, as were those under a section of the Mental Health Act 1983, or the Queensland Mental Health Act 2000 in the Australian arm, at the time of assessment.

Main outcome measures
The primary outcome measure was the reduction in aggressive episodes between baseline and after 4 weeks of treatment, measured using the Modified Overt Aggression Scale (MOAS). Secondary outcome measures included the Aberrant Behaviour Checklist (ABC), the Uplift/Burden Scale, the 40-item Quality of Life Questionnaire (QOL-Q), adverse drug effects using the Udvalg for Kliniske Undersøgelser (UKU) scale and severity of illness using the Clinical Global Impressions (CGI) scale. These were all completed at baseline, 4, 12 and 26 weeks by independent researchers. Modified Overt Aggression Scale scores were also recorded at weekly intervals from key workers over the 26-week period. Full economic
costs using a modified version of the Client Service Receipt Inventory (CSRI) were recorded for the 6 months before and after randomisation.

**Ethics**

Written informed consent was obtained, based on information that was understandable to the individuals concerned. For those who were not able to give informed consent, relevant carers, including relatives and senior staff at supported homes or related residential settings, were approached to assent to the trial. Consent was given in writing and witnessed.

**Procedure**

Patients likely to be suitable for the trial were identified by referring clinicians in the areas chosen for the study, and were registered for the study if they appeared to satisfy the inclusion criteria. Once identified, a researcher from the Neuroleptics in the treatment of Aggressive Challenging Behaviour for people with Intellectual Disabilities (NACHBID) team, together with health professionals involved in care, obtained consent and assent where necessary and then completed baseline assessments. Patients were randomised to placebo, risperidone or haloperidol using a permuted blocks procedure. Patients were treated initially with 1 mg risperidone/2.5 mg haloperidol/ placebo daily, which was increased, if necessary, to 2 mg risperidone or 5 mg haloperidol daily by 4 weeks, with further treatment in flexible dosage administered for a further 8 weeks. Treatment was continued from 12 to 26 weeks using the trial medication, unless the clinician or patient felt that this was no longer necessary or unless further treatment was indicated. Because some clinicians preferred to start with a lower dose (0.5 mg risperidone or 1.25 mg haloperidol) in view of concern about extra sensitivity to adverse effects in those with intellectual disability, the protocol was subsequently changed to allow this. Doses greater than two tablets per day (> 2 mg risperidone or 5 mg haloperidol) were allowed in exceptional circumstances, and lorazepam up to 2 mg daily (but no other medication) was permitted as ‘rescue’ medication in emergencies.

**Statistical methods**

We calculated that, using a 5% significance level, we needed data on 99 patients in order to have 80% power to detect a clinically relevant reduction in MOAS score of 8 points (standard deviation 11.4) between two treatments. In anticipation of a 20% drop-out rate we therefore planned to recruit 124 patients, with 99 expected to complete. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 14 and R Version 2.4.1. Univariate analyses were carried out using either the Mann–Whitney or Kruskal–Wallis test for comparing the value of continuous variables between two or more treatment groups. The Fisher exact test was used to compare the value of categorical variables between groups. Multivariate analyses of continuous outcomes were by regression, adjusting for baseline values of the response variable where appropriate. Analysis was by intention to treat, imputing missing values by last observation carried forward.

The main analysis was an intention-to-treat analysis of MOAS scores of the three treatment groups at week 4 using a quasi-likelihood approach, whereby the logarithm of mean MOAS score is assumed to be a linear function of significant predictors and where the variance is estimated from the data. We adjusted for logarithmically transformed baseline MOAS value and any other significant candidate predictors.

**Results**

There were considerable difficulties in recruitment because of ethical and consent doubts, but 86 patients, predominantly male (62%) (one of borderline intellectual disability, 30 with mild, 41 with moderate and 14 with severe intellectual disability), with similar distribution by randomised group, were recruited to the trial between November 2002 and July 2006. The patients were recruited from North and South London, Birmingham, Leicester, Nottingham, Newcastle, Gateshead, Cumbria, Cardiff and Brisbane, Queensland, Australia. Twenty-two clinicians recruited patients, with three (ZA, AR and SC) recruiting 40 patients between them.

The mean daily dosage for risperidone was 1.07 mg rising to 1.78 mg, and for haloperidol was 2.54 mg rising to 2.94 mg. Aggression declined dramatically with all three treatments by 4 weeks, with placebo showing the greatest reduction (79%, versus 57% for combined drugs) \((p = 0.06)\). Furthermore, although there were no important differences between the treatments, including adverse effects, at any of the time points, the placebo-treated patients showed no evidence of inferior
response to the patients receiving neuroleptic drugs, either singly or together. The recruitment rate was lower than expected and an additional study investigating the problems experienced in recruiting patients was carried out. It was found that those clinicians who had not participated in clinical trials before were less likely to recruit than others, but there were no other important differences.

Cost-effectiveness

The mean total cost of accommodation, services, informal care and treatment over the 6 months of the trial was £16,336 for placebo, £17,626 for haloperidol and £18,954 for risperidone. It is concluded that placebo is the most cost-effective treatment for aggressive challenging behaviour.

Conclusions

There is no evidence from this trial that either risperidone or haloperidol, given in conventionally low doses, offers any advantages over placebo in either the short- or medium-term treatment of aggressive challenging behaviour in intellectual disability, and over 4 weeks placebo was found to be more effective in reducing aggression. Placebo treatment is also cheaper in terms of total costs than the other two treatments over a 6-month period.

Implications for health care

The current use of neuroleptic drugs for the treatment of aggressive challenging behaviour in intellectual disability needs to be reviewed. The findings suggest that much of this prescribing may be unnecessary.

Recommendations for research

While neuroleptic drugs may be of value in the treatment of aggressive behaviour in some patients with intellectual disability, the underlying pathology needs to be evaluated before neuroleptic drugs are given. The specific diagnostic indications for such treatment require further investigation. The common practice of prescribing low doses of neuroleptic drugs in intellectual disability on the grounds of greater responsiveness and greater liability to adverse effects also needs to be re-examined.

Trial registration

This trial is registered as ISRCTN 11736448.

Publication

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Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/07/02. The contractual start date was in August 2002. The draft report began editorial review in April 2008 and was accepted for publication in October 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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