Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities

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 Eliahoo[13] and B North[13]

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

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

Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al*. Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID). *Health Technol Assess* 2009;**13**(21).

How to obtain copies of this and other HTA programme reports
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

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.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.