Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial

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Summary

Background Aggressive challenging behaviour is frequently reported in adults with intellectual disability and it is often treated with antipsychotic drugs. However, no adequate evidence base for this practice exists. We compared flexible doses of haloperidol (a typical, first-generation antipsychotic drug), risperidone (an atypical, second-generation antipsychotic), and placebo, in the treatment of this behaviour.

Methods 86 non-psychotic patients presenting with aggressive challenging behaviour from ten centres in England and Wales, and one in Queensland, Australia, were randomly assigned to haloperidol (n=28), risperidone (n=29), or placebo (n=29). Clinical assessments of aggression, aberrant behaviour, quality of life, adverse drug effects, and carer uplift (positive feelings about the care of the disabled person) and burden, together with total costs, were recorded at 4, 12, and 26 weeks. The primary outcome was change in aggression after 4 weeks' treatment, which was recorded with the modified overt aggression scale (MOAS). Analysis was by intention to treat. This study is registered as ISRCTN 11736448.

Findings 80 patients had adherence of 80% or more to prescribed drug. Aggression decreased substantially with all three treatments by 4 weeks, with the placebo group showing the greatest change (median decrease in MOAS score after 4 weeks=9 [95% CI 5–14] for placebo, 79% from baseline; 7 [4–14] for risperidone, 58% from baseline; 6·5 [5–14] for haloperidol, 65% from baseline; p=0·06). Furthermore, although no important differences between the treatments were recorded, including adverse effects, patients given placebo showed no evidence at any time points of worse response than did patients assigned to either of the antipsychotic drugs.

Interpretation Antipsychotic drugs should no longer be regarded as an acceptable routine treatment for aggressive challenging behaviour in people with intellectual disability.

Lancet 2008; 371: 57–63
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Introduction

People with intellectual disability often have poor resilience to adversity, and their ability to deal with stresses is also limited. One of the most common results of this limitation is the response of aggression and related challenging behaviour. Such behaviour is common, with a prevalence ranging from 16% to more than 50% depending on definition;[1–3] yet despite behaviour being used frequently as a clinical diagnosis it has no formal diagnostic status, and no clear connections to psychotic illness.[4]

Since the earliest report of the efficacy of antipsychotic (neuroleptic) drugs in this population,[5] the use of these drugs has become commonplace, with between 22% and 45% of people with intellectual disability in hospital and about 20% of those in the community being prescribed antipsychotic drugs.[6–8] These figures are very high considering that the prevalence of psychiatric illness in intellectual disability, which in previous studies has ranged from 28% to 46%,[7,9] falls to less than 15% when the pseudodiagnosis of problem behaviours is removed.[4] The difference in these figures suggests either that some of the antipsychotic drugs prescribed for people with intellectual disability are given for behavioural disturbance without underlying psychiatric illness, or that challenging behaviour ought to be regarded as an important diagnosis in its own right.

Despite the widespread use of antipsychotic drugs to treat challenging behaviour, the evidence base is scarce. A systematic review of antipsychotic drugs for the treatment of people with both challenging behaviour and intellectual disability found eight randomised controlled trials of antipsychotic drugs versus placebo but concluded that these studies "provided no evidence of whether antipsychotic medication helps or harms adults with intellectual disability and challenging behaviour".[10] The NACHBID (Neuroleptics for Aggressive CHallenging Behaviour in Intellectual Disability) clinical trial was designed to remedy this deficiency by comparing the effects of first-generation and second-generation antipsychotic drugs with placebo in people with intellectual disability who have shown disruptive behaviour.

Methods

Study design and patients

The study was a three-arm, parallel-group pragmatic trial of placebo, haloperidol, and risperidone with balanced randomisation, but no stratification, into each arm, and blind assessments of outcome at 4, 12, and 26 weeks after

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randomisation. The main null hypothesis was that there were no differences between the effects of a typical antipsychotic drug (haloperidol), an atypical antipsychotic drug (risperidone), and placebo in reduction of aggression, when flexible doses of the drugs were given for 4 weeks, in non-psychotic patients with aggressive challenging behaviour. Secondary hypotheses were that there were no important differences between the effects of the three treatments on aggression at 12 and 26 weeks, and aberrant behaviour, quality of life, general improvement, effect on carers, and adverse drug effects at 4, 12, and 26 weeks.

Patients were recruited to the trial between Nov 6, 2002, and Aug 24, 2006. We included all patients being treated by services for intellectual disability (intelligence quotient <75), and asked referring consultants to be broad-based in selection of patients with all degrees of severity of intellectual disability, and to consider recruiting those who had been given antipsychotic drugs in the past, but no longer took them. We excluded only those who had previously been clinically diagnosed as having a psychosis. A possible autistic spectrum disorder was not an exclusion criterion, provided that a clinical diagnosis of psychosis was absent. However, we excluded patients who had taken depot antipsychotic drugs, or any other injected antipsychotic drugs, within the past 3 months or continuous oral antipsychotic drugs within the past week, or those under a section of the Mental Health Act, 1983, (or the Queensland Mental Health Act, 2000 in the Australian group) at the time of assessment. Randomised patients agreed to take the study drug for 12 weeks, with the option of continuing until 26 weeks, unless at 12 weeks other options were preferred by clinician or patient. Adherence with prescribed drugs was recorded by counting the remaining tablets at each assessment visit.

Written informed consent was obtained on the basis of information that was understandable to the individuals concerned, which sometimes included considerable explanation and representation of the trial in simple picture format, so that the notion of the study could be appreciated. For patients who were not able to give informed consent, we approached relevant carers, including relatives and care staff at supported homes or related residential settings, to give assent to the trial. Consent was given in writing and witnessed.

Assessments

The main outcome of aggressive behaviour was recorded with the modified overt aggression scale (MOAS)[11]—a reliable measure in this population[12]—at baseline, 4, 12, and 26 weeks. MOAS scores were also recorded every week by telephone interview with the keyworkers of all patients over 26 weeks, with use of the agreed formulae for scoring. An independent researcher who was trained in the use of all instruments recorded other aspects of challenging behaviour with the aberrant behaviour checklist (community version),[13] effect on carers with the uplift and burden scale,[14] quality of life with the 40-item quality of life questionnaire,[15] adverse drug effects with the udvalg for kliniske undersogelser scale,[16] and severity of illness with the clinical global impression scale.[17] Scores were recorded at baseline, 4, 12, and 26 weeks. A screen for formal diagnosis of mental state diagnosis was completed by the relevant medical officer (usually a consultant) at baseline. The mini psychiatric assessment schedule for adults with developmental disability (PAS-ADD)[18] was used to identify patients within the autistic spectrum. The scores on the mini PAS-ADD were used for subsidiary analyses, not to include or exclude patients. All service contacts over the 6 months before and after randomisation were recorded with a modified version of the client service receipt inventory[19] at interview with a key informant of each patient (results will be reported elsewhere).

Procedures

Eligible participants with recent challenging behaviour and aggression (defined by at least two episodes of aggressive behaviour, with a total MOAS score of at least 4 in the past 7 days) were identified by 22 clinicians from ten sites in England and Wales (Cardiff, Newcastle, Gateshead, Nottingham, Leicester, Cumbria, and four sites in London), and one in Brisbane, Australia. All patients except one (in hospital) were recruited from community settings. After consent and assent from carers for inclusion in the study, baseline assessment was done for each patient by one of several independent researchers. Once assessed, each patient was randomly assigned to placebo, risperidone, or haloperidol by telephoning an independent colleague (at a separate location unconnected with any of the investigators) who allocated the patient by a permuted blocks procedure; a double-blind procedure was used subsequently throughout.

Patients were initially given tablets of identical appearance containing 1 mg of risperidone, 2·5 mg of haloperidol, or placebo daily, with increases if necessary up to 2 mg risperidone and 5 mg haloperidol daily by week 4, and maintenance treatment for a further 8 weeks, with the option of continuing treatment at this point up to 6 months. Some clinicians preferred to start with a lower dose (0·5 mg risperidone or 1·25 mg haloperidol) because of concern about extra sensitivity to adverse effects in people with intellectual disability, and thus the protocol was subsequently changed. Doses greater than two tablets a day (>2 mg of risperidone or 5 mg of haloperidol) were allowed in exceptional circumstances, and lorazepam up to 2 mg daily (but no other drug) was also permitted as a rescue medication in emergencies. Trial tablets were counted to check on dose taken at all assessment points.

Statistical analysis

We had initial difficulty in establishing a sample size, since the MOAS scale has not been used often in studies of intellectual disability. However, from our previous

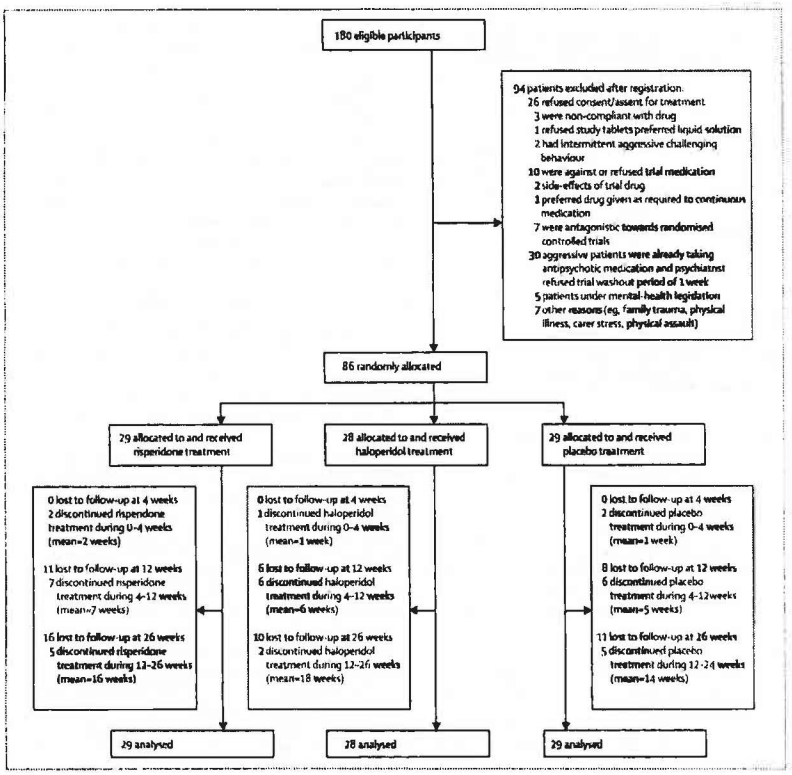

Figure 1: Trial profile

study of MOAS scores in this population,[9] we obtained means and standard deviations, and also developed a good idea of a clinically meaningful difference in scores. We calculated that with 96 patients allocated in total to the two active drugs (total number of patients needed in study=144), we had 80% power at the 5% level to detect a difference in MOAS score of 4, with a standard deviation of 8 and an unpaired *t* test with an allocation ratio of 2:1.

We used SPSS (version 14) and R (version 2.4.1) for the statistical analysis of completed data. Univariate analyses were done with the Mann-Whitney or Kruskal-Wallis tests for comparing the value of continuous variables between two or more treatment groups. We used the Fisher exact test to compare the value of categorical variables between groups. Multivariate analyses of continuous outcomes were by regression, with adjustment for baseline values of the response variable. Analysis was by intention to treat, imputting missing values by last observation carried forward. Comparisons of outcome were made between individual treatments and between the two active drugs and placebo, in the expectation that efficacy of the two active drugs would be much the same but adverse effects might differ.

The intention-to-treat analysis was the logarithm of weighted MOAS scores of the three treatment groups at week 4 with use of a quasi-likelihood approach, whereby the logarithm of mean MOAS score was assumed to be a linear function of significant predictors and the variance was estimated from the data. We adjusted for baseline MOAS value that was logarithmically transformed and

	Placebo (n=29)	Risperidone (n=29)	Haloperidol (n=28)
Age (years)	43 (34·5–55·5)	39 (28·5–44)	37·5 (26·25–50·75)
Men	17 (59%)	19 (66%)	17 (61%)
Centre			
London	12 (41%)	10 (35%)	11 (39%)
Wales	10 (35%)	9 (31%)	8 (29%)
Rest of England	5 (17%)	8 (28%)	7 (25%)
Australia	2 (7%)	2 (7%)	2 (7%)
Severity of intellectual disability			
Borderline	1 (3%)	0	0
Mild	11 (38%)	11 (38%)	8 (29%)
Moderate	12 (41%)	15 (52%)	14 (50%)
Severe (profound)	5 (17%)	3 (10%)	6 (21%)
Autistic spectrum	5 (17%)	6 (21%)	3 (11%)

Data are median (IQR) or number (%).

Table 1: Baseline characteristics

any other significant candidate predictors. No adjustment was made for multiple comparisons.

This study is registered as ISRCTN 11736448.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Of 180 eligible participants, 86 were randomly assigned to treatment groups. Table 1 shows the baseline characteristics, which were much the same between groups. Patients were predominantly men, and most had mild or moderate intellectual disability (table 1). At the fourth week of the study only one patient (assigned to placebo) had any missing data, and of the weekly MOAS assessments only three (different patients) of the 344 assessments were missing between baseline and week 4. Five (6%) patients discontinued their drug at some time before the assessment at week 4, a further 19 (22%) between weeks 4 and 12, and 12 (14%) between weeks 12 and 26 (figure 1). We noted only three serious problems with adverse effects leading to withdrawal—one patient with a known history of epilepsy had an epileptic fit after 8 weeks of haloperidol treatment (2·5–5 mg daily), one taking haloperidol had respiratory problems on a dose of 2·5 mg in the first week of treatment thought to be an anaphylaxis-linked reaction, and one taking risperidone (1–2 mg) became very distressed by headaches and agitation thought to be due to the drug after 5 weeks.

The tablet counts showed that most of the patients had treatment adherence of 80% or more with prescribed dose, with only two in each of the three treatment groups not achieving this level. The mean daily dose of risperidone was initially 1·07 mg, and increased to 1·78 mg; that of haloperidol was initially 2·54 mg, and increased to 2·94 mg. 61 (71%) patients completed follow-up at 12 weeks and 49 (57%) at 26 weeks (figure 1); analysis of data with last observation carried forward for missing data yielded no significant differences. Rescue medication with lorazepam was given for three (10%) patients allocated to placebo, six (21%) to risperidone, and two (7%) to haloperidol in the first 4 weeks, and to similar numbers in all groups between weeks 4 and 26 (nine [31%] placebo, seven [24%] risperidone, and seven [25%] haloperidol). Costs in the three groups will be reported separately.

The diagnostic assessment showed that 36 (42%) of the 86 patients did not cross the threshold for consideration of any formal diagnosis, and only 14 (16%) had any of the features of autistic spectrum disorders (table 1). Baseline MOAS scores were comparable between groups, except that patients allocated to risperidone had higher scores for aggression than did patients on the other two treatments, but not for other aberrant behaviours

	Placebo (n=29)			Risperidone (n=29)			Haloperidol (n=28)		
	0 weeks	4 weeks	12 weeks	0 weeks	4 weeks	12 weeks	0 weeks	4 weeks	12 weeks
MOAS score	12 (8–25)	2·5* (0–6·5)	7 (0·25–12)	19 (12·5–28)	8* (2–22·5)	6 (0–14·5)	13 (8–30·75)	4·5* (0–19)	2 (0–5)
Much improved on CGI scale	..	8 (28%)	5 (19%)	..	7 (24%)	7 (27%)	..	7 (26%)	12 (46%)
ABC score (challenging behaviour)	51 (27·5–68)	21·5 (11–45)	29·5 (8–57)	46 (32–59)	25 (16–45·5)	25 (12·5–37·75)	50 (25·25–67)	35 (20·75–47·5)	24 (16–41)
Quality-of-life score	70 (64–72·5)	72 (65·7–77·75)	70 (63–77·5)	69 (57·5–82)	70 (60–78)	72 (65·75–80)	66 (58 25–72·5)	66 (59·5–75·5)	69 (59–76)
Uplift score	14 (11·25–16)	15·5 (12·5–17)	15 (11·5–16·5)	15 (13–16)	15 (13–16·5)	14·5 (12·75–17·25)	13·5 (12–15)	14 (12·25–16)	14 (12·75–16)
Burden score	26 (23–29)	24 (21·27·75)	23 (21·5–27)	26 (23–29·5)	24 (21·5–30)	25 (22–30 25)	27 (23·25–32·5)	27·5 (22·5–31)	24 (21·75–30·25)
UKU scale score (extrapyramidal effects)	3 (1·5–8·5)	4 (1–6·5)	3 (0–4·75)	4 (0·5–8)	3 (0–8)	1·5 (0–3·25)	5·5 (1–9·75)	3·5 (0·25–8·75)	3 (0–6)

Data are median (IQR) or number (%), but analyses used logarithmically transformed data. For all scales, high scores indicate greater effects. MOAS=modified overt aggression scale. CGI=clinical global impression. ABC=aberrant behaviour checklist. UKU=udvalg for kliniske undersøgelser. *For the primary outcome (differences between MOAS scores at 4 weeks adjusted for baseline differences): placebo vs risperidone p=0·07; placebo vs haloperidol p=0·14; placebo vs both active drugs p=0·06.

Table 2: Changes in aggression scores, global improvement, and other disruptive behaviour from baseline after 4 and 12 weeks of treatment

(table 2). The raw MOAS scores at 4 weeks showed a change in aggression in all treatment groups (median decrease in MOAS score after 4 weeks=9 [95% CI 5–14] for placebo, 79% from baseline; 7 [4–14] for risperidone, 58% from baseline; 6·5 [5–14] for haloperidol, 65% from baseline). Analysis of logarithmically transformed scores showed greater change for placebo than for the other two active drugs combined (p=0·06) after baseline differences were accounted for (table 2).

Analysis of MOAS scores every week (figure 2) showed that over the first week all three treatments were much the same, but that between week 2 and 4 the placebo group maintained the initial improvement better than did the active drug groups. Patients given placebo showed no evidence of a significantly worse response at any time points than did those assigned to either of the antipsychotic drugs (figure 2). Separate analysis of the autistic patients showed no evidence of a different response in this group, although the number of patients was small (data not shown). Six patients allocated to placebo, five to risperidone, and three to haloperidol had a screening diagnosis within the autistic spectrum; they had similar outcomes with the three drugs to those who screened negatively.

Secondary outcomes—including the aberrant behaviour checklist scale and its irritability factor score, and adverse effects recorded by the udvalg for kliniske undersogelser scale—all showed no differences between any of the drug treatments (table 2). At 4 weeks, the median irritability score had reduced from 26 to 12 (54%) with placebo, from 23 to 11 (52%) with risperidone, and from 23·5 to 17 (28%) with haloperidol. Table 3 shows the changes in aggression scores, global improvement, and other disruptive behaviour from baseline after 26 weeks of treatment. When drug effects were compared after 26 weeks, the median difference in MOAS scores was −8 (95% CI −18 to −4) in the placebo group, −10 (−17 to −8) in risperidone group, and −11 (−19 to −8) in haloperidol group; p=0·72). Since 12 patients received a lower dose than that planned in the original protocol (ie, <1 mg risperidone or <5 mg haloperidol daily) post-hoc analyses of differences were done in the other 74 patients only; we noted no important differences between the groups. Nor were there differences between the outcomes at any of the trial sites.

81 (4%) of the potential 2236 weekly MOAS assessments were missing, although we recorded no differences when these scores were replaced and reanalysed by last observation carried forward method.

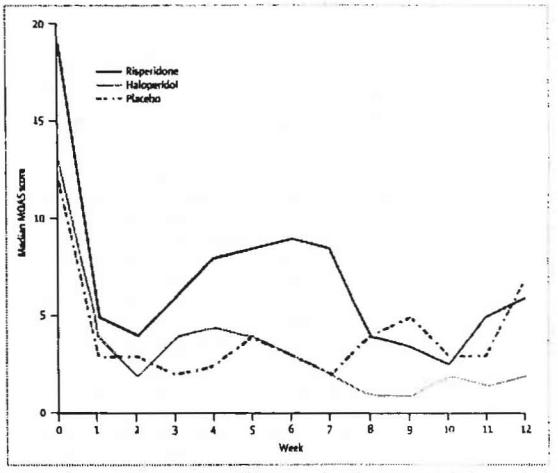

Figure 2: Median aggression scores on the modified overt agression scale (MOAS) during the first 12 weeks of the trial
Scores were logarithmically transformed before analysis.

	Placebo	Risperidone	Haloperidol
MOAS score	3·5 (1–7)	2 (0–12)	1 (0–5)
Much improved on CGI scale*	5 (25%)	5 (26%)	7 (33%)
ABC score (challenging behaviour)	28 (4–43)	33 (15–47)	26 (20–49)
Quality-of-life score	72 (62–79)	78 (70–80)	71 (65–77)
Uplift score	15 (14–16)	16 (13–17)	13 (12–16)
Burden score	24 (22–26)	28 (20–30)	29 (21–32)
UKU scale score (extrapyramidal effects)	2 (1–5)	3 (0–6)	2 (0–4)

Data are median (IQR) or number (%). Numbers in each treatment group vary for different outcomes. For all scales, high scores indicate greater effects. MOAS=modified overt aggression scale. CGI=clinical global impression. ABC=aberrant behaviour checklist, UKU=udvalg for kliniske undersogelser. No differences between any treatments were significant. *The CGI scale was assessed on everyone who was still in the trial (undertaken by keyworkers and therefore not dependent on patients).

Table 3: Changes in aggression scores, global improvement, and other disruptive behaviour from baseline after 26 weeks of treatment

Discussion

Our multicentre study has compared first-generation and second-generation antipsychotic drugs with placebo in patients with aggressive challenging behaviour. Although we noted a reduction in aggression with all treatments after 4 weeks, the greatest decrease was with placebo. Furthermore, we recorded no differences between groups in terms of aberrant behaviour, quality of life, general improvement, effect on carers, and adverse drug effects.

Our results differ from those of Van den Borre and colleagues[20] and Gagiano and co-workers,[21] who showed that risperidone, when used in similar or larger doses than in our study, was more effective than placebo in reduction of challenging behaviour measured by the aberrant behaviour checklist scale, with the irritability factor also showing drug differences. However, the degree of improvement in our sample in all groups of the trial was very great, with not only MOAS scores falling substantially, but also scores on the aberrant behaviour checklist scale. Thus Gagiano and colleagues reported

that risperidone, at similar doses to our study of 1–4 mg (mean 1·45 mg), reduced scores by 53% and placebo by only 31% after 4 weeks treatment, which was less than in our study over the same time period. Gagiano and co-workers, and several other investigators, used a placebo run-in period before randomly assigning patients to treatment, but this approach is not consistent with the main aim of a pragmatic trial, which is to reflect as much as possible the circumstances in ordinary practice.

Our study—which was undertaken in a population that is representative of people with intellectual disability, and which includes more patients with moderate and severe intellectual disability, for whom aggressive behaviour is more common, than other studies[4]—shows that either the placebo effect, the psychological effect of a formal external intervention, or spontaneous resolution, or all three, are substantial and would be difficult to surpass by even the most effective of drugs. The many practitioners involved in the study used doses that were lower than those used for similar purposes in adult psychiatry, since people with intellectual disability are sensitive to adverse effects. This practice is common[21] and is justified on the basis that organic brain dysfunction often results in idiosyncratic responses to psychotropic drugs. This notion suggests that small doses should be used initially, with close attention paid to any emerging side-effects. We noted no evidence of such abnormal sensitivity to antipsychotic drugs in our trial, except for the one patient with epilepsy who had a seizure with haloperidol. Although larger doses could have produced different effects, they would have had to be very great indeed to be significantly better than the substantial improvement shown with placebo after 4 weeks. The absence of any significant differences between drugs on any of the other secondary outcomes reinforces the conclusion that the antipsychotic drugs were of no selective benefit.

The number of participants recruited into the study was less than the planned target of 144, but this target assumed a drop-out rate of 20%, which was much greater than the very small drop-out rate that we recorded at 4 weeks. Thus, although the study failed to recruit its planned numbers despite a doubling of the recruitment period, the very low attrition rate and high adherence with prescribed drugs adds strength to our findings. Furthermore, since the differences between drugs at 4 weeks all favoured placebo, the argument that a larger sample might have detected an otherwise hidden drug effect is difficult to sustain, but nonetheless we accept the study was underpowered. We noted no evidence of a delayed beneficial effect of the active drugs over an increased period of time.

Our findings accord with the concerns expressed in a study undertaken 10 years ago that concluded there is "overuse of psychotropic medication to 'treat' challenging behaviour in people with intellectual disability, with symptoms of mental ill health failing to emerge as a key predictor of antipsychotic drug use".[1] They also suggest that ethical concerns, which although need to be addressed carefully, should not inhibit further randomised controlled trials of treatments in intellectual disability, since the outcomes could both increase benefit and prevent harm.[24] Our findings emphasise the dangers of treating challenging behaviour as though it were a precise, diagnostically useful sign, when it is heterogeneous and without diagnostic precision;[4] of associating it with specific management without knowledge of its natural history; and of regarding the results of open studies and small trials as an acceptable evidence base. The fact that more than two-fifths of patients did not even cross the threshold of a fairly sensitive screen for psychiatric disorder emphasises the dangers of treating a symptom or behaviour in isolation.

Our trial has shown that aggressive challenging behaviour in people with intellectual disability decreases whether or not active medication is given. The tendency for clinicians to give steadily reduced doses of antipsychotic drugs in such instances is then understandable, since the lower the dose the nearer the approximation to a placebo effect. Emerson's plea for psychological interventions, of which there are several now available,[25,26] seems to be fully justified, although there is still a shortage of good randomised trials of these interventions.

Our results should not be interpreted as an indication that antipsychotic drugs have no place in the treatment of some aspects of behaviour disturbance in people with intellectual disability. Evidence suggests that such drugs are effective for autistic behaviour disturbance in children[27] (although our trial had too few people in this group to test this separate hypothesis) and in prevention of further aggressive behaviour in those given antipsychotic drugs as an emergency measure;[28] treatment with benzodiazepines can also be crucial to effective management.[29] But we conclude that the routine prescription of antipsychotic drugs early in the management of aggressive challenging behaviour, even in low doses, should no longer be regarded as a satisfactory form of care.

Contributors

PT wrote the paper, was the grant holder and is guarantor of the study. PC and MM were the trial coordinators; MC, DM, and NB helped in trial design and monitoring. ZA, SC, SD, SB, MH, and DH were principal investigators at UK and Queensland sites; PO, MM, MH, BRe, KK, and SK were research assessors; ZA, AR, SC, and DT were involved in planning and as individuals referred the most patients; and BRa, BM, and JE did the data analysis. Glasgow MREC coordinated and approved the ethical applications.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank the National Coordinating Centre for Health Technology Assessment (NCCHTA), Southampton UK, for their funding of the NACHBID trial, but the views expressed are those of the authors alone. We thank the Mental Health Research Network, for adopting and promoting the trial in the UK, and the University of Queensland for hosting the trial in Australia; Freya Tyrer for background data; the UK

charity MenCap for supporting and promoting the trial; all individuals involved in this study at all levels, including Laure Lenôtre, Joanna Watson, and Jill Thompson who assisted in recruitment; the consultants who took part in recruitment, especially Angela Hassiotis and S Ganeshanathan; Ben Thrift and Malcolm Walker who diligently randomly assigned all the patients; the members of the Trial Steering Committee (Sheila Hollins, Stephen Tyrrr, and Angela Hassiotis), and the Data Monitoring and Ethics Committee (William Fraser, Tony Johnson, and Deborah Rutter) for their wise advice and support; and also people with intellectual disability and their carers who participated in this trial. The medication was provided by Janssen-Cilag, with additional costing of approximately £6000 spent on preparation of the medication for individual patients by the pharmacy staff of the main trial centre pharmacy.

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