A pilot randomised controlled trial of community-led ANtipsychotic Drug REduction for Adults with Learning Disabilities

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Scientific summary

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Background

There are approximately 200,000 adults in England and Wales with a registered learning disability (LD). Rates of antipsychotic medication prescribing in this population are high (approximately 50,000 adults with LDs) and far exceed the estimated prevalence of psychosis (3–4%). It is known, however, that antipsychotics are commonly prescribed for challenging behaviour, and prescription rates for adults with LDs cluster around 50%. However, There is little evidence to support the effectiveness of antipsychotic medications for this indication and side effects include cardiovascular events, central/autonomic nervous system and endocrine function side effects, akathisia and other movement disorders, weight gain and increased risk of type 2 diabetes mellitus. Recent National Institute for Health and Care Excellence guidance acknowledges the limited evidence available to support use of antipsychotic medication for management of challenging behaviour in adults with a LD, and it states that antipsychotics should be prescribed only if psychological interventions and/or treatment for comorbid conditions have been unsuccessful or there is significant risk to the individual or others.

There has been a recent drive from NHS England to review antipsychotic prescribing in this population, as a result of the Winterbourne Review. The Royal College of Psychiatrists has also issued a report on psychotropic drug prescribing in this population, recommending regular review of treatment response and side effects. There is some existing, although limited, evidence from unblinded studies that these medications can be safely reduced or withdrawn, without a corresponding increase in challenging behaviour.

Objectives

The primary objective of the trial as originally designed was to evaluate the impact of a blinded antipsychotic medication withdrawal programme in adults with LDs without psychosis compared with treatment as usual. More specifically, the aim was to determine whether or not withdrawal could be safely achieved without a corresponding increase in aggression, as indicated in previous non-blinded studies. The primary outcome (aggression) was to be assessed at baseline and 9 months (blinded), with levels of aggression compared between arms. A secondary objective was to explore potential non-efficacy-based barriers to drug reduction in clinical practice via qualitative interviews with principal investigators (PIs), carers and participants. However, community-led ANtipsychotic Drug REduction for Adults with Learning Disabilities (ANDREA-LD) is reported here as an exploratory pilot trial and the primary objectives were revised to assess feasibility of recruitment and retention and to explore non-efficacy-based barriers to reduction. A revised secondary objective was to compare trial arms regarding clinical outcomes.

Methods

The ANDREA-LD trial was designed as a large-scale non-inferiority trial of an antipsychotic withdrawal programme in primary care. However, owing to significant challenges, the focus of recruitment shifted to community learning disability teams (CLDTs). The trial closed early and is reported as an exploratory pilot study. The study population was adults (aged $\geq$ 18 years) with recognised LDs without psychosis who are prescribed risperidone or haloperidol for challenging behaviour. However, the number of potential participants prescribed haloperidol was much lower than expected and so only those taking risperidone were recruited. Follow-up was reduced from 12 months to 9 months. Informed consent was provided by participants themselves, if judged to have capacity, or by a personal (or professional if required) legal representative.

Interventions

Participants in the intervention arm progressed through up to four approximately equal reduction stages to full withdrawal within a 6-month period, while the control group maintained baseline treatment. All trial medication was encapsulated to maintain the blind. Sites were supported by a detailed treatment and safety package. Treatment achieved at 6 months was maintained for a further 3 months under blind conditions. At 9 months, following collection of follow-up data, the blind was broken and participants and PIs were informed of treatment allocation and current dosage.

Outcome measures

Screening

Intelligence quotient (IQ) and current psychosis were assessed at screening using the Adaptive Behaviour Scale (ABS) and the Mini Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD) interview, respectively. Participants were eligible provided they did not score > 70 on the ABS and/or > 2 on the Mini PAS-ADD checklist.

Main outcome measures

Feasibility outcomes were (1) the number and proportion of general practices/CLDTs that progressed from initial approach to recruitment of participants and (2) the number and proportion of recruited participants who progressed through the various stages of the study. We also compared trial arms regarding the following clinical outcomes:

- Modified Overt Aggression Scale (MOAS; primary outcome as originally designed), level of psychotropic medication use, the Aberrant Behaviour Checklist (ABC) and the PAS-ADD checklist to monitor mental health at 6 and 9 months post randomisation.
- The Antipsychotic Side-effect Checklist (ASC) and the Dyskinesia Identification System Condensed User Scale (DISCUS) to assess movement disorders, use of other interventions to manage challenging behaviour (e.g. seclusion, physical restraint) at 9 months post randomisation.
- Use of as-required [pro re nata (PRN)] medication.
- The Client Service Receipt Inventory (CSRI) was modified for use in learning disability to collect data on services used and support received by participants.

Study visits and assessments

Participants had five appointments with the PI: four to review appropriateness of progression to the next stage and a final one for unblinding. Participants/carers collected study medication from the practice nurse or pharmacist monthly. Eligibility data were collected at screening. All data collection was carried out face-to-face either at site or during home visits.

Statistical methods

Randomisation and unblinding

Randomisation was based on minimisation and allocations balanced on medication dose (< 4 mg of risperidone/at least 4 mg of risperidone) and recruitment source (general practice/CLDT). Participants were randomised in a 1 : 1 ratio. Non-routine unblinding was performed only after authorisation from the chief investigator or clinical reviewer.

Sample size

The planned sample size was 310 participants [90% power, 95% confidence interval (CI), non-inferiority margin of 3, effect size of 0.375] and was adjusted for 20% attrition. However, in the revised pilot study no specific sample size was set and 22 participants were recruited over 19 months until early closure of the trial.

Quantitative analysis plan

The original proposed primary analysis focused on a comparison between the arms of MOAS scores at the 9-month follow-up. However, for the pilot study, we focused on estimating the following feasibility outcomes: (1) the number and proportion of primary care practices/CLDTs that progressed from initial approach to recruitment of participants and (2) the number and proportion of recruited participants who progressed through the various stages of the study. We also compared trial arms at 6 and 9 months post randomisation on (1) MOAS, (2) level of psychotropic medication use, (3) ABC and (4) PAS-ADD checklist and at 9 months only on (1) ASC, (2) DISCUS and (3) other interventions to manage challenging behaviour. Information was also collected on use of PRN medication over the study period and costs and service utilisation at 6 and 9 months post randomisation.

Analysis of recruitment and retention outcomes was descriptive. Clinical outcomes were compared between arms using regression models (linear or logistic), adjusting for baseline scores and balancing variables (dose and recruitment route). MOAS score at 9 months post randomisation was fitted with a two-sided 90% CI in order to reflect the planned primary analysis and individual trajectories for MOAS scores were plotted and described, with particular attention paid to individuals whose MOAS scores changed by at least 4 points (i.e. who were clinically meaningful).

The original proposed cost-effectiveness analysis focused on comparison of trial arms through calculation of incremental cost-effectiveness ratios, defined as the difference between trial arms in mean costs divided by the difference in mean outcome (MOAS score) over 9 months. It was proposed to conduct the main cost-effectiveness analyses from health and social care agencies and a wider societal perspective to include health and social care agencies and unpaid carers. To inform the cost-effectiveness analyses, it was proposed that comprehensive data on health, social care and other services used by individuals were included in the study. This was done using a tailored version of the CSRI. However, planned cost-effectiveness analyses were not carried out given the very small sample size.

Qualitative study

We undertook qualitative interviews with a proportion of carers, PIs and participants. A key aim was to gain insight into non-efficacy-based barriers to drug reduction in clinical practice, as well as attributions of behavioural changes in relation to perceived reduction of medication. Interviews were scheduled to take place during the unblinded phase of the trial between 9 and 12 months. For the pilot study, these were brought forward to 4–6 months post randomisation. The purpose of the interviews was to ascertain (1) views about participating in the study, (2) reasons for partial or full reinstatement of medication after unblinding and (3) views about antipsychotic medication use to control challenging behaviour. PI interviews focused on views of the support package and how patients/carers managed during the trial. Interview topics for participants focused on (1) reasons for participating, (2) how they felt they managed during the trial and (3) views about taking medicines to help with behaviour. All interviews were audio-recorded, transcribed, anonymised and analysed using thematic analysis facilitated by NVivo version 10 (QSR International, Warrington, UK).

Results

Recruitment and retention

Approximately 500 potential sites were approached to take part in the trial, of which 79 expressed an interest (the majority of which were CLDTs). Thirty-six participants were screened and 22 were randomised

(61.1%: 80% of those screened and 100% of those who completed a baseline assessment from primary care and 61.3%/95% from community LD teams). Participants were well balanced with respect to variables collected pre randomisation and clinical scores were generally low at baseline. The majority of participants were on a total daily dose of risperidone of < 4 mg, and were recruited from CLDTs. Arms were well balanced with respect to these key variables. Of the 22 participants randomised, 13 (59.1%) achieved progression through all four stages of reduction (potential reduction in control arm). Follow-up data at 6 and 9 months post randomisation were obtained for 17 participants (77.3% of those randomised), with 10 intervention and seven control participants followed up. Participants who progressed to stage 4 tended to be older, had higher MOAS, ABC-lethargy, and ABC-hyperactivity scores at baseline, were more likely to have their challenging behaviour managed using PRN medication prior to randomisation and were less likely to have a diagnosis of autism spectrum disorder.

Clinical outcomes

Modified Overt Aggression Scale total scores were higher at 6 months than at baseline and higher 9 months post randomisation than at 6 months, remaining higher in the intervention arm in both modified intention-to-treat and per-protocol populations. For most participants, change in MOAS total scores was slight. However, five participants experienced a change from baseline in MOAS total score of at least 4. Scores for secondary outcome measures were also generally slightly higher in the intervention arm at 6 and 9 months, including other challenging behaviour (ABC subscales), mental health (PAS-ADD checklist), movement disorders (DISCUS, 9 months only) and PRN use (although diary completion rates were low). Reported side effects were higher in the control arm, and antipsychotic medication use at 6 and 9 months was lower in the intervention arm. It is difficult to draw conclusions from the limited data on use of other interventions to manage challenging behaviour. Four adverse events and one serious adverse event were reported.

Qualitative results

The results suggest that carers, participants and clinicians agreed on the importance of the research question, that study procedures were acceptable and that support from the research team was good. Generally, there was a feeling that the study should be supported by the LD community, but there was also an awareness of the challenges involved in doing this. Issues that caused more concern included consenting arrangements (particularly carers' concerns about acting as a personal legal representative), whether or not the study inclusion and exclusion criteria were appropriate (e.g. whether or not to include participants with autism) and the size of the overencapsulated study medication. In addition, carers in particular reported that participants experienced a number of negative behaviours during the study period. However, these behaviours were not always attributed to drug reduction, even by carers, and many behaviours were not new within the study period.

Conclusions

Recruitment of this population, within primary care in particular, is challenging. In general, this is largely a result of difficulty in identifying appropriate persons to consent and carer concerns regarding re-emergence of challenging behaviour. In primary care, low numbers of potentially eligible participants per practice and general practitioner (GP) concerns relating to safety were also a significant factor. Carer and GP concerns were probably exacerbated by limited availability of alternative (behavioural) interventions to manage behaviour. It is not, therefore, feasible to recruit this population to a drug reduction programme within primary care. Although recruitment in CLDTs was more successful, it is still unlikely that the target sample size would have been achievable in a reasonable time frame, without provision of alternative interventions to manage behaviour.

Although it is not possible to draw firm conclusions from the small sample size in the current trial, results indicate that drug reduction is possible and likely to be safe in the majority of cases. However, low-level changes were observed in behavioural and mental health measures and in the development of movement

disorder in some participants, suggesting that focused support and alternative interventions are required. We therefore recommend that guidance is produced to support practitioners, carers and patients in this process. The results of the qualitative study provide important insights into the experiences of people taking part in drug reduction studies that should influence future trial development. First, it seems that reported barriers to recruitment did not reflect the experience of those recruited to the study. Second, study procedures were acceptable, and complex issues such as blinding and overwrapping of medication were not particularly problematic.

The results also provide information of value to those wishing to conduct further high-quality interventional randomised controlled trials in people with a LD. We have shown that carers and participants coped well with fairly complex trial processes. This study suggests that, although there is a clear need, primary care services are not currently well equipped to deliver this type of intervention. This is important for other studies, which should explore the clinical competencies needed and how these apply to primary care if that is where the target population predominantly receive health care. We also recommend that measures are put in place to improve recruitment to studies in people with a LD. Despite increasing guidance on the use of antipsychotic medication, no guidance exists for reducing this medication. This pilot study has provided valuable insights into the development of such guidance for clinicians and carers and, beyond this, to support improved access to trials for people with a LD.

Trial registration

This trial is registered as ISRCTN38126962.

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