Community led ANti-psychotic Drug REduction for Adults with Learning Disabilities (ANDREA-LD): a randomised double-blind placebo controlled pilot trial

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Background

- 200,000 adults in England/Wales with registered learning disability (LD)
- Antipsychotic prescribing rates exceed prevalence of psychosis (3-4%)
- Prescribed for challenging behaviour but little effectiveness evidence
- Side effects include: cardiovascular, central/autonomic nervous system function, movement disorders, weight gain & >risk of T2 diabetes
- NICE guidance acknowledges limited evidence & recommends antipsychotics only if psychological interventions unsuccessful or significant risk to individual/others
Post-Winterbourne drive from NHS England to review antipsychotic prescribing

Royal College of Psychiatrists report recommends regular review of response & side effects

Some evidence (unblinded studies) that medication can be reduced/withdrawn without corresponding increase in challenging behaviour

Need for controlled trial of impact of phased, blinded withdrawal on dosage, behaviour, psychiatric symptoms, safety & treatment costs
Objectives

• Primary objective: evaluate impact of blinded withdrawal vs. treatment as usual on aggression

• Secondary objective: explore non-efficacy based barriers to drug reduction via qualitative interviews (PIs, carers, participants)

• Reported as exploratory pilot trial due to significant recruitment issues

• Revised objectives:
  – Primary: feasibility of recruitment & retention; non-efficacy based barriers
  – Secondary: compare trial arms on clinical outcomes
Methods

• Designed as non-inferiority trial of antipsychotic withdrawal in primary care but recruitment shifted to community LD teams

• Population: adults (18+); LD without psychosis; prescribed risperidone for challenging behaviour

• Consent given by participants with capacity, or personal/professional legal representative

• Up to 4 approx. equal reduction stages to full withdrawal in 6m period; control group maintained baseline treatment (9m follow-up)

• Medication encapsulated to maintain blind; sites supported by treatment & safety package
Outcomes

• Feasibility outcomes:
  – no. GP practices/LD teams progressing from approach to participant recruitment
  – no. participants progressing through reduction stages

• Clinical outcomes (6&9m):
  – Aggression (MOAS); psychotropic medication use; challenging behaviour (ABC); mental health (PAS-ADD); medication side-effects (ASC); movement disorders (DISCUS); use of e.g. seclusion, physical restraint; use of as required (PRN) medication; services used/support received
• 1:1 randomisation balanced on dose (<4mg/≥4mg risperidone) & recruitment source (GP/Community LD team)

• Planned sample size: 310 adjusted for 20% attrition

• For revised pilot study no sample size set; 22 participants recruited
## Results: feasibility outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary care</th>
<th>LD teams</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contacted</td>
<td>470</td>
<td>30</td>
<td>500</td>
</tr>
<tr>
<td>Expressed interest</td>
<td>59</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>Identified potentially eligible participants</td>
<td>41</td>
<td>20</td>
<td>61</td>
</tr>
<tr>
<td>Provided a participant who was screened</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Provided a participant who was randomised</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary care</th>
<th>LD teams</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>5</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Completed baseline</td>
<td>3</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Randomised</td>
<td>3</td>
<td>19</td>
<td>22</td>
</tr>
</tbody>
</table>
### Results: feasibility outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Control</th>
<th>Intervention</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total randomised</strong></td>
<td>11 (100.0)</td>
<td>11 (100.0)</td>
<td>22 (100.0)</td>
</tr>
<tr>
<td><strong>Intervention receipt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0 to Stage 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrew before S1</td>
<td>2 (18.1)</td>
<td>1 (9.1)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Progressed from S0-1</td>
<td>9 (81.8)</td>
<td>10 (90.9)</td>
<td>19 (86.4)</td>
</tr>
<tr>
<td>Stage 1 to Stage 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrew between S1&amp;2</td>
<td>3 (27.3)</td>
<td>1 (9.1)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Delayed progression between S1&amp;2</td>
<td>0 (0.0)</td>
<td>2 (18.1)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Progressed from S1-2</td>
<td>6 (54.5)</td>
<td>7 (63.6)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>Stage 2 to Stage 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrew between S2&amp;3</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Delayed progression between S2&amp;3</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Progressed from S2-3</td>
<td>6 (54.5)</td>
<td>7 (63.6)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>Stage 3 to Stage 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrew between S3&amp;4</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Progressed from S3-4</td>
<td>6 (54.5)</td>
<td>7 (63.6)</td>
<td>12 (59.1)</td>
</tr>
<tr>
<td>Participant follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed 6m follow-up</td>
<td>7 (63.6)</td>
<td>10 (90.9)</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td>Completed 9m follow-up</td>
<td>7 (63.6)</td>
<td>10 (90.9)</td>
<td>17 (77.3)</td>
</tr>
</tbody>
</table>
Results: feasibility outcomes

• Participants who progressed to Stage 4:
  – older
  – higher baseline scores for aggression & other CB (lethargy, hyperactivity)
  – ASD diagnosis less likely

• Well balanced on pre-randomisation variables; baseline clinical scores low; majority on total daily dose <4mg risperidone
Results: clinical outcomes

• MOAS scores >6m than baseline in intervention arm & >9m than 6m:
  – MITT control mean = 3.7 (SE = 3.55), intervention mean = 7.7 (SE = 3.51)
  – PP control mean = 4.3 (SE = 4.14), intervention mean = 9.3 (SE = 4.94)

• For most change was slight but clinically meaningful for 5 participants

• Secondary outcome scores slightly higher in intervention arm at 6&9m
  (challenging behaviour; mental health; movement disorders; PRN use)

• Side effects higher in controls

• Limited data on other interventions to manage challenging behaviour

• 4 adverse events (AE) and 1 serious adverse event (SAE) reported
Qualitative interviews

- 16 carers (5 parents & 11 professional; face-to-face/telephone); 8 professionals (telephone); 4 participants (face-to-face)
- Thematic analysis with abductive approach (NVivo 10)
- Carers, participants & clinicians agreed study procedures were acceptable & that they were well-supported by research team
- General feeling that study should be supported by LD community BUT aware of challenges involved
Importance

Carer 24 (parent):

“I’ve really enjoyed it because I think it is opened up to you (to) sort of look at other people, ‘should they be on this? Should they be on that? Can we reduce that?’”

Carer 9 (staff):

“….so everyone was more aware so it could be awareness of you know if we see any anxiety building up then this is what we do to help him to calm. Possibly a different approach to managing the behaviour.”

Clinician 6:

”...obviously it’s a contentious area and we need a definitive answer one way or the other....I’m very aware of people...on antipsychotic medication because of bad episodes, remain on it for many years later without it being adequately reviewed."
Non-efficacy based barriers

• Carer concerns about acting as personal legal representative:

  Clinician 3: “We did spend quite a lot of time trying to find out who was the proper person to discuss informed consent and talk about informed consent...it was very clear that the carers could give full consent, but the reality was that the carers were not happy, were quite uneasy with that.”

• Whether inclusion criteria were appropriate:

  Clinician 7: “....we do have patients with autism and sometimes they’re on small doses of antipsychotics and trying to, although it’s not for a psychosis, it’s for other reasons, so I think they may have been included. And when they’re taken off, even a small dose of antipsychotics they had difficulties I think, so that maybe something, that they’re a slightly separate population to people without autism.”
Non-efficacy based barriers

• Size of study medication:

  Carer 57 (staff): “Maybe the tablet could be a bit smaller because it is quite a bit of a horse pill to take.”

• Carer reports that participants experienced negative behaviours during study period; not always attributed to drug reduction & many not newly occurring within study period
Some positive changes

Participant 52:

“I feel quite um, I’ve had a bit of changes yeah”

Interviewer:

“Ok, in what way?”

Participant 52:

“um... I don’t necessarily want to hurt myself so much”
Conclusions

- Drug reduction possible and safe:
  - BUT low level changes in behaviour, mental health & development of movement disorder in some: focused support/interventions needed

- Recommend guidance produced to support practitioners, carers & patients in reduction/withdrawal
  - Increasing guidance on use of antipsychotics but none for reduction

- Qualitative results provide insights into experiences of people taking part that should influence future trial development
  - Study procedures acceptable & complex issues (blinding, overwrapping) not particularly problematic
Conclusions

• Whilst there is clear need, primary care not well equipped to deliver this type of intervention

• Future studies should explore clinical competencies needed & how these apply to primary care (if where target population receive healthcare)

• Recommend measures to improve recruitment to LD trials & consider how adults with LD could be included in general population trials
  – e.g. commitment from RC Psych for mandatory GCP training; performance-related measures linked to recruitment to LD studies
Thank you

Project team:
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