Update on the evidence to support deprescribing

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Director – London & South East Medicine Information Service

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To cover the following

• Evidence that it isn’t harmful....
• Evidence that it does some good.....
• Controversial areas
  • Bisphosphonates
  • PPIs
  • Anti-diabetes medicines
• STOPPFrail recommendations
• Economics of deprescribing
Evidence that it isn’t harmful

The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis.


• 132 papers (n= 34143 participants) – randomised and observational studies that involved deprescribing one or more medicines in older people.

• Robust literature search and methodology

• Randomised studies that assessed impact on mortality (n=10, 3151 participants) showed no significant impact on mortality (OR 0.82, 95% CI: 0.61 to 1.11) however when restricted to interventions applied at the individual patient level (n=8, 1906 participants) it was associated with a reduction in mortality (OR 0.62, 95% CI: 0.43 to 0.88). Educational interventions has no impact (OR 1.21 (0.86 to 1.69)

• Non-randomised studies (n=2, 257 participants) showed a significant decrease in mortality (OR 0.32, 95%CI: 0.17 to 0.6)

• Subgroup analysis based on age, single medication/class withdrawal, cognitive status showed no significant differences in terms of impact on mortality/
Other findings

Mortality associated with deprescribing interventions to reduce antipsychotic medications in randomized studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H Random, 95% CI</th>
<th>Odds Ratio M-H Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Ballard 2004</td>
<td>3 81</td>
<td>7 66</td>
<td>63.3%</td>
<td>1.03 [0.25, 5.17]</td>
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<tr>
<td>Ballard 2008 &amp; Ballard 2009</td>
<td>27 62</td>
<td>39 64</td>
<td>69.4%</td>
<td>0.47 [0.21, 0.95]</td>
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<tr>
<td>Davies 2012</td>
<td>3 52</td>
<td>7 60</td>
<td>57.8%</td>
<td>0.81 [0.45, 1.45]</td>
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<tr>
<td>Ruts 2004</td>
<td>3 27</td>
<td>1 28</td>
<td>64.4%</td>
<td>3.18 [0.33, 31.65]</td>
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<tr>
<td>Van Reekum 2002</td>
<td>1 17</td>
<td>2 15</td>
<td>10.5%</td>
<td>0.44 [0.04, 6.94]</td>
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</tr>
</tbody>
</table>

Total (95% CI) 222 / 221: 100.0%
Number of falls per participant associated with deprescribing interventions to reduce polypharmacy in randomized studies
Other findings

Adverse drug withdrawal effects associated with deprescribing interventions to reduce antipsychotic medications in randomized studies

Systolic blood pressure associated with deprescribing interventions to reduce diuretics in randomized studies
Other findings

Successful withdrawal associated with deprescribing interventions to reduce benzodiazepine use in randomized studies

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<tr>
<td>6.17.1 Benzodiazepine</td>
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<tr>
<td>Carrau 2002</td>
<td>19</td>
<td>55</td>
<td>74</td>
<td>34.2%</td>
<td>0.77 [0.29, 2.00]</td>
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<tr>
<td>Petrovic 2002</td>
<td>12</td>
<td>20</td>
<td>32</td>
<td>30.9%</td>
<td>0.38 [0.09, 1.54]</td>
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<tr>
<td>Tamminga 2014</td>
<td>40</td>
<td>148</td>
<td>188</td>
<td>54.9%</td>
<td>7.95 [3.38, 18.35]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>223</td>
<td>224</td>
<td>447</td>
<td>100.0%</td>
<td>1.18 [0.21, 6.08]</td>
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<tr>
<td>Total events</td>
<td>62</td>
<td></td>
<td>84</td>
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<tr>
<td>Heterogeneity Tau² = 2.46; CH² = 10.55, df = 2 (P = 0.0011); I² = 50%</td>
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Non-vertebral fractures associated with deprescribing interventions to cease bisphosphonates in non-randomized studies

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<tr>
<td>da Silva 2011</td>
<td>1</td>
<td>40</td>
<td>41</td>
<td>3.8%</td>
<td>1.94 [0.08, 49.41]</td>
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<tr>
<td>Exner 2011</td>
<td>0</td>
<td>30</td>
<td>30</td>
<td>3.8%</td>
<td>0.33 [0.01, 9.71]</td>
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<tr>
<td>Watts 2008</td>
<td>19</td>
<td>398</td>
<td>417</td>
<td>100.0%</td>
<td>0.96 [0.49, 1.87]</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>468</td>
<td>417</td>
<td>885</td>
<td>100.0%</td>
<td>0.94 [0.50, 1.78]</td>
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<tr>
<td>Heterogeneity Tau² = 0.00; CH² = 0.59; df = 2 (P = 0.75); I² = 0%</td>
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Evidence that it isn’t harmful

Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis


Twenty-five studies, including 10 980 participants, were included, comprising 21 randomized controlled trials and four nonrandomized controlled trials
Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis
Evidence that it does some good

Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review.


12 studies (n= 22438 - 8 RCTs, 2 cluster RCTs and 2 controlled before and after studies)
Evidence that it does some good

• Impact on hospital admission
  • 2 studies reported no impact, 3 studies reported some reduction. Meta-analysis not possible
  • Similar finding reported in BJCP meta-analysis – 2 studies positive, 6 studies no significant difference and no meta-analysis possible

• Improvement in mortality?
  • BJCP meta-analysis based on low quality evidence estimated that for every 1000 patients that undergo a strategy to reduce polypharmacy – a statistically non-significant 5 less patients will die within the a follow up period of between 2 and 18 months (but 95% CI extends from a reduction of 16 deaths to an increase of 22)
Evidence that it does some good

- Improvement in medication appropriateness
  - Based on 4 RCTs - summated MAI score (-)6.78, 95% CI (-)12.34 to (-)1.22. But marked heterogeneity – I squared- 96%
  - Based on 2 studies – intervention patients prescribed fewer Beers drugs than control patients. Mean difference (-)0.1 (95% CI: (-) 0.28 to (+) 0.09 but marked heterogeneity
  - Two studies assessed impact on STOPP medicines both showed a reduction but data not pooled
  - BJCP analysis – showed a difference in the number of inappropriate medicines prescribed of 0.49 (95%CI: 0.28 to 0.7) (3 studies – 839 participants)
Evidence that it does some good

• Reduction in number of medicines taken
  • BJCP meta-analysis reported a mean reduction of 0.99 medicines per patient (95%CI: 0.14 to 1.83) (based on 2 studies and 451 participants)

• Impact on quality of life
  • In general - no evidence that deprescribing is associated with significant changes in quality of life using standardised measures although one study showed a significant but modest impact in terms of slowing decline in quality of life (MD 0.3 – 1 study, 189 participants)
Stopping PPIs

• Deprescribing versus continuation of chronic pump inhibitor use in adults. Cochrane Database Systematic Reviews 2017; Issue 3

• Review of 6 trials with 1758 participants
• 5 trials assessed on-demand prescribing and 1 assessed sudden cessation
• Low quality evidence indicates that on-demand use increases risk of “lack of symptom control compared with continuous use (RR 1.71 – 95%CI 1.31 to 2.22)
• Moderate quality evidence that on-demand use leads to a reduction in pill burden of 3.79 doses per week (2.84 to 4.73)
• Low quality evidence that on-demand dosing is associated with reduced patient satisfaction
Stopping bisphosphonates

FDA - Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee (2011)

• Limited fracture data on bisphosphonate exposure out to 10 years appear to demonstrate that there is sustained but no further increase in fracture benefit after 3-4 years of therapy but also no clear evidence of harm or increase in overall osteoporotic fractures. While different subsets of patients appear to have evidence of benefit with continued therapy, these findings are dependent on the study reviewed. There is no clear subset of patients that has clear benefit with continued therapy confirmed across multiple studies. In patients who discontinue bisphosphonate exposure after 3-5 years of treatment, fracture incidence rates were relatively constant over time.
Stopping antihyperglycaemics


• Only 2 controlled before and after studies – both deemed to be low quality
  • One study of an educational intervention aimed at pharmacists showed that use of glibenclamide could be reduced (by switching or stopping) without compromised glycaemic control in community-dwelling older people [actual difference 0.06% in HbA1c – 95%CI: -0.16 to 0.12%] (n= 4368)
  • One study showed that if oral antihyperglycemics and insulin (<=20units per day) were discontinued (or if >20 units reduced by 50%) in nursing home residents (n=32) there was a non-significant 1.1% (0.56% lower to 1.64% higher) increase in HbA1c and no significant impact on mortality (RR 0.74, 95%CI: 0.29 to 1.87).
STOPPFrail: consensus validation

• Published in Age and Ageing 2017; 46: 60-627

• List of potentially inappropriate prescribing indicators in older patients (≥ 65 years) who meet all of these criteria
  • End stage irreversible pathology
  • Poor one year survival prognosis
  • Severe functional impairment and/or severe cognitive impairment
  • Symptom control is the priority rather than prevention of disease progression
List of medicines for review includes

- Lipid lowering medicines
- Alpha blockers for hypertension
- Anti-platelets for primary prevention
- Neuroleptics antipsychotics
- Memantine
- PPIs and H2 antagonists
- GI antispasmodics
- Theophylline
- Calcium supplements
List of medicines for review includes

- Antiresportive, SERMs and bone anabolic medicines
- Long-term NSAIDs
- Long-term corticosteroids
- Diabetic oral agents – aim for monotherapy
- ACEIs or ARBs for prevention diabetic nephropathy
- Multivitamins
- Nutritional supplements
- Prophylactic antibiotics
The economics of deprescribing

Health economics analysis of polypharmacy reviews (www.polypharmacy.scot.nhs)

• Estimated that number of patients aged 75 years and older, receiving a high-risk medicine and estimated to be at 40-60% risk of admission/readmission equates to 747 patients per 100,000 population

• Additionally estimated that number of patients aged 50 years and over resident in a care home and taking medicine equates to 580 per 100,000 population

• As a combined population potentially eligible for medication review this equates to 1221 per 100,000 population (ie 1.2% population)
The economics of deprescribing

Cost avoidance

• If one drug with an average unit cost of £9.87 (and an average 6 repeats) is stopped for one year – this would reduce prescribing costs by ~£72,000 per 100,000 population (of which ~£45,000 is in the over 75 years cohort)

• If two drugs are stopped these estimates are doubled (ie £144,000 per 100,000 popn of which £90,000 is in the over 75’s cohort)

• If cost estimates extended to include switching to more cost effective medicines and removal of duplicate prescriptions cost avoidance increases to between £109,000 and £189,000 per 100,000 population.

• It is estimated that the cost of hospitalisation due to avoidable ADRs is between £58,500 and £407,000 per 100,000 population
The economics of deprescribing

Costs incurred

• If we assume a review requires 1.46 hours pharmacist time, 0.63 hours physician time and 0.5 hours of nurse/pharmacist to undertake implement and follow-up – this equates to £114 per review including on-costs.

• Based on previous numbers this requires £140,000 per 100,000 population of staff time (of which £89,000 is focussed on 75+ years cohort)

• Bottom line – even focussing on the highest risk populations the costs avoided and costs incurred are likely to be similar unless reviews lead to a reduction in health service utilisation (especially hospitalisation) and/or include a wider consideration of cost-effective prescribing.