What is the evidence for deprescribing in older people?

National Workshop on Deprescribing
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Northern Clinical School, Sydney Medical School
IN OLDER PATIENTS

› Supportive evidence
  - Evidence of safety of medicines
  - Evidence of efficacy of medicines

› Direct evidence
  - Evidence of safety of deprescribing
  - Evidence of efficacy of deprescribing
SUPPORTIVE EVIDENCE
Medicines less safe in older people
Pharmacoepidemiology Important for Drug Safety and Serious Adverse Events Increase in Old Age

SAEs Reported to FDA 1998-2005

**Table 3. Age Burden of Serious Adverse Events, 1998-2005**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Serious Events, %</th>
<th>Total Population, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Expected Cases, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>7.4</td>
<td>25.8</td>
<td>13.8</td>
</tr>
<tr>
<td>18-44</td>
<td>25.3</td>
<td>39.4</td>
<td>31.2</td>
</tr>
<tr>
<td>45-64</td>
<td>33.7</td>
<td>22.2</td>
<td>31.4</td>
</tr>
<tr>
<td>≥65</td>
<td>33.6</td>
<td>12.6</td>
<td>23.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Age group percentage of total from standard 2000 US population.

<sup>b</sup> Percentage of population total, adjusted for likelihood of medication use.

Moore et al., Arch Intern Med 2007
Hospital admissions coded as 2º to ADRs in WA

**A: Age-standardised rates by sex**
- Men
- Women

**B: Age-specific rates**
- 80+ years
- 70-79 years
- 60-69 years

*Burgess et al MJA 2005*
Why do ADEs increase with age?

Reduction in organ function

Altered pharmacokinetics

Altered pharmacodynamics

Reduced homeostatic function

Adverse effects

Multiple diseases

Multiple prescribers

Multiple medicines

Poor adherence

Prof Andrew McLachlan
Less evidence of efficacy in older people
Only 3% of published randomised, controlled trials and 1% of meta-analyses include people over 65 years.

Even if trials do not exclude on chronologic age, they do so on comorbidity, comedications and/or physical and cognitive function (biologic age/frailty).

What is the evidence for efficacy in older people

› Evidence from “older frail people’s” RCTs – limited
› Evidence from “older people’s” RCTs
› Evidence from “younger people’s” RCTs
› Observational pharmaco-epidemiology
› “N of 1” trials
› Logical interpretation of pathophysiology
› Pre-clinical evidence
› Learn from trainers/mentors, ie expert opinion

Consider evidence in context of competing causes of morbidity and mortality and patient’s goals of care
Why are medications ceased in practice?

› Avoid or prevent adverse drug reactions: Non-maleficence
  - common in older people with serious clinical outcomes

› Limited medication efficacy: Beneficence
  - often no evidence base in older people or evidence suggests lack of efficacy
DIRECT EVIDENCE OF SAFETY AND EFFICACY OF DEPREScribing
Medication Withdrawal Trials in People Aged 65 Years and Older
A Systematic Review

Shoba Iyer,¹ Vasi Naganathan,¹ Andrew J. McLachlan¹² and David G. Le Couteur¹

- All trials 1996-2007
- Over 65 yrs, withdrawal of a single medicine
- 31 studies
- N=8972 subjects
- Variety of open label, observational, randomised, placebo controlled studies
## Results - trial design

<table>
<thead>
<tr>
<th>Class</th>
<th>Randomised placebo controlled</th>
<th>Randomised no placebo</th>
<th>Prospective observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (n=448)</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antihypertensive (n=7188)</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Psychoactive (n=1184)</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Results

› Diuretics
  - 4 studies, 448 subjects
  - Successful 51-100% subjects (recommenced mainly if heart failure)

› Antihypertensives
  - 9 studies, 7188 subjects
  - 20-85% normotensive over following 6-60 mths

› Psychotropics
  - 15 studies, 1184 subjects
  - ↓ falls ↑ cognition and/or behaviour

› Withdrawal syndromes
  - None reported and medicines often weaned over weeks
Best quality evidence of safety and efficacy: withdrawal of benzodiazepines used as hypnotics and withdrawal of antipsychotics used for BPSD
The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial

Clive Ballard, Maria Luisa Hanney, Megan Theodoulou, Simon Douglas, Rupert McShane, Katja Kossakowski, Randeep Gill, Edmund Juszczak, Ly-Mee Yu, Robin Jacoby, for the DART-AD investigators

Withdrawal of antipsychotics Reduces mortality by ~40% but borderline significance and small numbers
9 trials (7 in Nursing homes) 606 subjects

8 of 9 no difference in success of withdrawal between groups

We recommend that programmes that aim to withdraw older nursing home residents from long-term antipsychotics should be incorporated into routine clinical practice, especially if the NPS are not severe”
Implementation/ effectiveness studies for benzodiazepines and antipsychotics
Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education: The EMPOWER Cluster Randomized Trial

Cara Tannenbaum, MD, MSc; Philippe Martin, BSc; Robyn Tamblyn, PhD; Andrea Benedetti, PhD; Sara Ahmed, PhD

Table 2: Prevalence, Risk Difference, and Odds Ratios for Discontinuation and Discontinuation Plus Benzodiazepine Dose Reduction at the 6-Month Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants, No.</th>
<th>Outcome, No. (%)</th>
<th>Risk Difference (95% CI)a</th>
<th>No. Needed to Treat</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)b</th>
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</thead>
<tbody>
<tr>
<td>Discontinuation of benzodiazepine use</td>
<td></td>
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<tr>
<td>Intention to treat analysis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>148</td>
<td>40 (27.0)</td>
<td>0.23 (0.14-0.32)</td>
<td>4.35</td>
<td>8.05 (3.51-18.47)</td>
<td>8.33 (3.32-20.93)</td>
</tr>
<tr>
<td>Usual care</td>
<td>155</td>
<td>7 (4.5)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intraclass correlation</td>
<td></td>
<td>0.008</td>
<td>0.008</td>
<td>0.010</td>
<td></td>
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<tr>
<td>Per protocol analysis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intervention</td>
<td>123</td>
<td>38 (30.9)</td>
<td>0.26 (0.16-0.36)</td>
<td>3.85</td>
<td>8.53 (3.69-19.76)</td>
<td>8.10 (3.34-19.66)</td>
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<tr>
<td>Usual care</td>
<td>138</td>
<td>7 (5.1)</td>
<td></td>
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<tr>
<td>Intraclass correlation</td>
<td></td>
<td>0.007</td>
<td>0.007</td>
<td>0.005</td>
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<tr>
<td>Discontinuation plus benzodiazepine dose reduction</td>
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<tr>
<td>Intention to treat analysis</td>
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<td></td>
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<tr>
<td>Intervention</td>
<td>148</td>
<td>56 (37.8)</td>
<td>0.27 (0.18-0.37)</td>
<td>3.70</td>
<td>5.05 (2.66-9.59)</td>
<td>5.49 (2.78-10.84)</td>
</tr>
<tr>
<td>Usual care</td>
<td>155</td>
<td>17 (11.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraclass correlation</td>
<td></td>
<td>0.006</td>
<td>0.006</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol analysis</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>123</td>
<td>54 (43.9)</td>
<td>0.34 (0.22-0.45)</td>
<td>2.94</td>
<td>6.33 (3.10-12.92)</td>
<td>6.73 (3.12-14.55)</td>
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<tr>
<td>Usual care</td>
<td>138</td>
<td>16 (11.6)</td>
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<tr>
<td>Intraclass correlation</td>
<td></td>
<td>0.030</td>
<td>0.030</td>
<td>0.020</td>
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</tr>
</tbody>
</table>

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*a* 95% Confidence intervals were calculated using robust standard errors.

*b* Adjusted for age, sex, education, health status, indication of benzodiazepine use for insomnia, anxiety disorder, benzodiazepine dose, previous attempt at tapering, duration of benzodiazepine use, and number of medications.
Families count cost of dementia drugs prescriptions

Australian Broadcasting Corporation
Broadcast: 16/08/2012
Reporter: Margot O'Neill

Up to 6,000 elderly people could be dying prematurely each year because of widespread over-prescription of anti-psychotic drugs to dementia patients in nursing homes.

Transcript
Deprescribing antipsychotics for behavioural and psychological symptoms of dementia

HALT

Longitudinal study design

**Primary objective:** Reduce use of antipsychotic medication in aged care residents, without increase in substitute psychotropic drugs

**Intervention:** involves study pharmacist, patient’s GP, medicare local GP, nursing home champion, nursing training

CI: Prof Henry Brodaty, UNSW

Funding: Australian Government Department of Social Services under the Aged Care Service Improvement and Healthy Ageing Grant Fund.
Deprescribing psychotropics in long term care

RedUSe: Reducing Use of Sedatives and Aged Care Facilities

› Involves RACFs and their staff, GPs, the supply community pharmacy, as well as the pharmacist providing the QUM services for the RACF.

› Multi-strategic, includes:
  - audits of sedative use
  - educational sessions for nursing staff
  - ‘good practice’ guidelines
  - academic detailing for GPs attending the RACF
  - information provided to relatives and residents
  - involvement of NPS MedicineWise and the PSA

› CI: Juanita Westbury, University of Tasmania

› Funded by Australian Government Department of Social Services under the Aged Care Service Improvement and Healthy Ageing Grant Fund.
EVIDENCE FOR DEPREScribing MULTIPLE DRUGS FROM MULTIPLE CLASSES IN THE SETTING OF POLYPHARMACY
The war against Polypharmacy: A New Cost-Effective Geriatric-Palliative Approach for Improving Drug Therapy in Disabled Elderly People

Doron Garfinkel MD\textsuperscript{1}, Sarah Zur-Gil MA\textsuperscript{2} and Joshua Ben-Israel MD\textsuperscript{3}

\textsuperscript{1}Department of Evaluation & Rehabilitation, \textsuperscript{2}Pharmacy, and \textsuperscript{3}Directorate, Shoham Geriatric Medical Center, Pardes Hana, Israel

- 6 nursing departments
- stop or reduce as many drugs as possible using an algorithm
- Examples: nitrates stopped if not chest pain for 3 months, H2 blockers stopped if no bleeding or symptoms for 12 months, K and Fe supplements, antihypertensives
- Failure of withdrawal defined
- Not randomised

\textit{IMAJ} 2007;9:430–434
Success rate after one year follow-up according to types of drugs discontinued

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>No of pts drug stopped</th>
<th>Failures (signs/symptoms)</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>22</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>H2 Blockers</td>
<td>35</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>51</td>
<td>9</td>
<td>82</td>
</tr>
<tr>
<td>Diuretics</td>
<td>27</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>15</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Potassium Supps</td>
<td>20</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Iron Supps</td>
<td>19</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>Sedatives</td>
<td>16</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>19</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>13</td>
<td>4</td>
<td>69</td>
</tr>
</tbody>
</table>

**BETTER CLINICAL OUTCOMES**
- One year mortality rate: 45% control group vs 21% study group (p < 0.001)
- Annual referral rate to acute care facilities: 30% control group vs 11.8% study group (p < 0.002)
Mean Age 83

Recommended discontinuation of 311 medications in 64 patients (4.4 drugs/patient)

Discontinuation achieved in 88%

No ADWEs
Frusemide | Symptoms of CCF
---|---
H2 Blocker | Dyspepsia
L-DOPA | Parkinsonism
Antihyperten | BP > 160/90 or 150/90 if target organ damage
Iron Supps | Anaemia
Potassium supps | Hypokalaemia

Defined Intervention

**Defined Intervention Failure**

Discuss the following with the patient/guardian

- An evidence-based consensus exists for using the drug for the indication given in its current dosing rate in this patient's age group and disability level, and the benefit outweighs all possible known adverse effects
- Indication seems valid and relevant in this patient's age group and disability level
- Do the known possible adverse reactions of the drug outweigh possible benefit in old, disabled patients?
- Any adverse symptoms or signs that may be related to the drug?
- Is there another drug that may be superior to the one in question?
- Can the dosing rate be reduced with no significant risk?

Yes
- Stop drug
- Introduce another drug

No
- Continue with the same dosing rate
- Reduce dose

Arch Intern Med. 2010;170(18):1648-1654
Need higher quality evidence of safety and efficacy of deprescribing in the setting of multimorbidity and polypharmacy
A randomized controlled trial of deprescribing to optimize medical therapy for frail older people: The Opti-med Study

NHMRC Project $1,444,996 over 5 years

CIs: Beer, Potter, Hilmer, Naganathan, McLachlan, Commans

Primary aim to determine whether deprescribing is safe among older people living in residential aged care facilities (RACF)
Secondary Outcomes

› Quality of life
› Anticholinergic and sedative drug exposure (DBI)
› Number of potentially inappropriate medicines
› Number of regular and PRN prescription medicines
› Hospital admissions
› Independence in activities of daily living
› Cognitive function
› Falls
› Fractures
Double blind RCT with open intervention arm

Uses encapsulation to hide medication

Protocol driven medication reduction based on Garfinkel
  - derived by trial pharmacists

Up to 1,000 participants

Randomised to:
  - blinded control group
  - blinded intervention group
  - open intervention group

Most outcomes measured at 3, 6, 9 and 12 months

ADWE monitored 1 week after any possible change in medication
Target high risk medications with less obvious functional effects: DBI as a trigger to deprescribe

Drug Burden Index: cumulative exposure to anticholinergic and sedative medicines associated with functional impairment

Development of Drug Burden Index calculator

Feasibility study with Home Medicines Review

Primary Aim: Reduce DBI

Secondary Aim: Improve function

<table>
<thead>
<tr>
<th></th>
<th>DBI decreased</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>6/19 (32%)</td>
</tr>
<tr>
<td>Control</td>
<td>6/31 (19%)</td>
</tr>
</tbody>
</table>

https://www.drugburdenindex.com

Gnjidic et al., Annals of Pharmacotherapy, 2010
Lisa Kouladjian, PhD student
What’s the evidence for deprescribing in older people?

- Limited for both safety and efficacy for most deprescribing interventions (level III or IV)
- Strongest for antipsychotics in BPSD (level I)
- Evidence being generated currently for safety, efficacy and implementation of deprescribing interventions