

RESEARCH PAPER

Deprescribing to optimise health outcomes for frail older people: a double-blind placebo-controlled randomised controlled trial—outcomes of the Opti-med study

CHRISTOPHER ETHERTON-BEER¹, AMY PAGE¹, VASI NAGANATHAN², KATHLEEN POTTER³, TRACY COMANS⁴, SARAH N. HILMER², ANDREW J. MCLACHLAN², RICHARD I. LINDLEY², DEE MANGIN^{5,6}

¹WA Centre for Health and Ageing, University of Western Australia, M577, 35 Stirling Hwy, Crawley WA 6009, Australia

²Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

³Operations, Ryman Healthcare, Christchurch, Canterbury, New Zealand

⁴Centre for Health Services Research, University of Queensland, Brisbane, Australia

⁵Family Medicine, McMaster University, Hamilton, Canada

⁶General Practice, University of Otago, Christchurch, New Zealand

Address correspondence to: Christopher Etherton-Beer; E-mail: christopher.ether-ton-beer@uwa.edu.au

Abstract

Background: potentially harmful polypharmacy is very common in older people living in aged care facilities. To date, there have been no double-blind randomised controlled studies of deprescribing multiple medications.

Methods: three-arm (open intervention, blinded intervention and blinded control) randomised controlled trial enrolling people aged over 65 years ($n = 303$, noting pre-specified recruitment target of $n = 954$) living in residential aged care facilities. The blinded groups had medications targeted for deprescribing encapsulated while the medicines were deprescribed (blind intervention) or continued (blind control). A third open intervention arm had unblinded deprescribing of targeted medications.

Results: participants were 76% female with mean age 85.0 ± 7.5 years. Deprescribing was associated with a significant reduction in the total number of medicines used per participant over 12 months in both intervention groups (blind intervention group -2.7 medicines, 95% CI $-3.5, -1.9$, and open intervention group -2.3 medicines; 95% CI $-3.1, -1.4$) compared with the control group (-0.3 , 95% CI $-1.0, 0.4$, $P = 0.053$). Deprescribing regular medicines was not associated with any significant increase in the number of 'when required' medicines administered. There were no significant differences in mortality in the blind intervention group (HR 0.93, 95% CI 0.50, 1.73, $P = 0.83$) or the open intervention group (HR 1.47, 95% CI 0.83, 2.61, $P = 0.19$) compared to the control group.

Conclusions: deprescribing of two to three medicines per person was achieved with protocol-based deprescribing during this study. Pre-specified recruitment targets were not met, so the impact of deprescribing on survival and other clinical outcomes remains uncertain.

Keywords: deprescribing, residential aged care facilities, ageing, older people

Key Points

- Deprescribing using a structured medication withdrawal plan results in reduced number of medications.
- Double-blind trials deprescribing multiple medications are feasible through encapsulating medicines targeted for cessation.
- Mortality and clinical outcomes appear to be similar in intervention groups, whether open or blind, compared with controls.

Introduction

Over one-third of older people are prescribed at least five medicines, and for people with dementia living in residential aged care facilities (RACFs), the prevalence is over 90% [1]. Deprescribing is an intervention that aims to reduce the harms associated with inappropriate polypharmacy by identifying and ceasing medicines that no longer benefit the patient [2]. When medicines are withdrawn deliberately under supervision, during a formal deprescribing process, adverse withdrawal effects are detected early and, if necessary, can be ameliorated by restarting the withdrawn medications or a more suitable alternative [3–5]. Current evidence indicates that deprescribing interventions are safe and that individualised patient-specific deprescribing interventions may be associated with reduced mortality [6].

The evidence base for deprescribing interventions in residential care [7] is currently limited to open or single-blinded studies. We previously enrolled 95 RACF residents and reported a significant decrease in polypharmacy (2.0 ± 0.9 medicines per participant) with no significant adverse impact on mortality or other health outcomes [8]. Although these open data are promising, the absence of blinded data is an important limitation, given the biases associated with studies of medication use, including both placebo and nocebo effects. In one seminal trial in people living in their own homes [9], 47% of patients in the withdrawal group had restarted their medications 1 month after unblinding, despite having been successfully withdrawn and ‘treated’ with placebo for the prior 30 weeks of the study.

The aim of this study was to investigate whether deprescribing affects survival and quality of life in older people living in RACF in a randomised double-blind controlled trial. We evaluated a deprescribing intervention which, if found to be safe and efficacious (in the blinded study), and effective (in the open arm), would be suitable for implementation by general practitioners (GPs) or trained pharmacists acting in partnership with GPs in routine care settings, thus influencing policy and practice.

Methods

Ethics

Ethical approval for this study was from the University of Western Australia (WA) and Concord Repatriation General Hospital (NSW) ethics committees (RA/4/1/5930 and HREC13/CRGH/77). The study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12613001204730; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365059>) and the World Health Organization (Universal Trial Number U1111-1148-6,094).

Study design

A randomised double-blind placebo-controlled trial with an additional open intervention arm was conducted.

Participants were randomly allocated to one of three groups: a blinded control group, blinded intervention (deprescribing) group and open intervention (deprescribing) group. Blinding was by over-encapsulation of medication. A blinded study design was chosen to assess and control for placebo, and nocebo, effects. We included an open deprescribing group to also determine the practical benefits of reducing the number of doses physically taken (‘pill burden’), as there would be no change in the number of ‘medicines’ taken if a participant was randomised to the blind deprescribing group or blind control group (as placebo was used to maintain the total number of doses). Participants in the open deprescribing group would however take fewer doses if the intervention was successful.

Patient and public involvement

The study steering committee overseeing the study included consumer and industry representatives.

Participants

People aged 65 years and older who lived in participating RACF, were taking at least one regular medication and spoke English were included. People were excluded if they were moribund or otherwise in the terminal phase of illness with a short life expectancy or the RACF manager or usual general practitioner did not consent to their participation. We gained residents’ informed consent to participate and/or the agreement of the next of kin or person responsible.

Baseline assessment

Trained research assistants measured sitting and lying heart rate and blood pressure and collected the baseline demographic, clinical and medication data using self-report and/or facility records, reconciled with a second source (e.g. a staff informant, GP report, RACF medical record). Participant assessments included the Mini-Mental State Examination (MMSE) [10] and Modified Barthel Index (MBI) [11]. A Frailty Index was calculated [12]. Staff informants rated behavioural and psychological symptoms of dementia using the Neuro-Psychiatric Inventory (NPI) [13]. Quality of life was self-rated using the EQ-5D-5L [14, 15]. Participants who were able to complete the Beliefs About Medicines Questionnaire [16]. The frequency and severity of common medication side effect symptoms (nausea, constipation, diarrhoea, abdominal pains, dry mouth, dizziness, headaches, insomnia, skin rash or itch, cough, ankle swelling and dry eyes) were rated using a tool we developed previously [8] (not yet validated). Staff informants rated the Medication Side Effects screen and EQ-5D-5L for participants unable to complete these.

Development of medication withdrawal plans

The study intervention has been described in detail previously [17] and is summarised briefly. Medicines were targeted for withdrawal according to a structured deprescribing

protocol previously described [8, 18, 19]. Two research pharmacists independently reviewed all participants' solid dose form oral medications taken regularly and *pro re nata* (PRN) medicines used at least weekly to generate a list of target medications for withdrawal using the deprescribing algorithm. Medicines least likely to be of benefit to the participant and least likely to cause adverse drug withdrawal events (ADWEs) were planned to be ceased first and those most likely to cause ADWEs and/or more likely to be providing some symptomatic benefits were planned to be tapered slowly and withdrawn last. When tapering was required, doses were generally halved at fortnightly intervals until a dose of half the lowest dose form was reached, following which the medication was ceased. Medications with long half-lives were reduced to every second and/or every third day dosing until ceased. Up to three medications were withdrawn simultaneously if unlikely to cause ADWEs or if withdrawal effects would be clearly ascribable to the individual drugs. The research pharmacists resolved any differences in the medication withdrawal plan by consensus. The final medication withdrawal plan listed each participant's target medications, rationale for deprescribing and the order in which they were to be tapered/ceased if the participant was randomised to an intervention arm. It documented a monitoring plan and details of potential ADWE for each target medication.

GP agreement to medication withdrawal plan

Prior to randomisation, the GP was given the medication withdrawal plan for participants in all groups and asked to reconfirm their agreement for randomisation and withdrawal of each target medication. The GP could 'veto' any part of the medication withdrawal plan.

Randomisation and allocation concealment

Participants were randomised after the consensus medication withdrawal plan and GP assent were completed. Randomisation was carried out centrally by a bio-statistician using computer-generated randomisation tables. Only the statistician and the study pharmacist encapsulating the study medicines were aware of group allocation. All participants, research assistants, RACF staff, relatives, GPs and investigators who had any contact with study participants in the blind control or blind intervention groups and/or study data remained blind to treatment allocation.

Medication supply and encapsulation

Inert capsules in a range of diameters, lengths and opaque colours were used to over-encapsulate solid dose form tablets or capsules to achieve blinding during medication withdrawal. Pharmacists selected appropriately sized capsules and, where possible, matched colour of capsule to the tablet or capsule. In cases where similar tablets required encapsulation, the intention was to allow the encapsulated products to be distinguishable. For example, if two medicines that

are both small red tablets required encapsulation, the second tablet was encapsulated in a capsule of different colour or size. This procedure allowed individual medicines to be identified if required. Ceased medications were replaced with a placebo capsule and continued until the end of the study. In the blinded control group, the tablets identified as potential target medicines for deprescribing were over-encapsulated to maintain blinding.

Monitoring during implementation

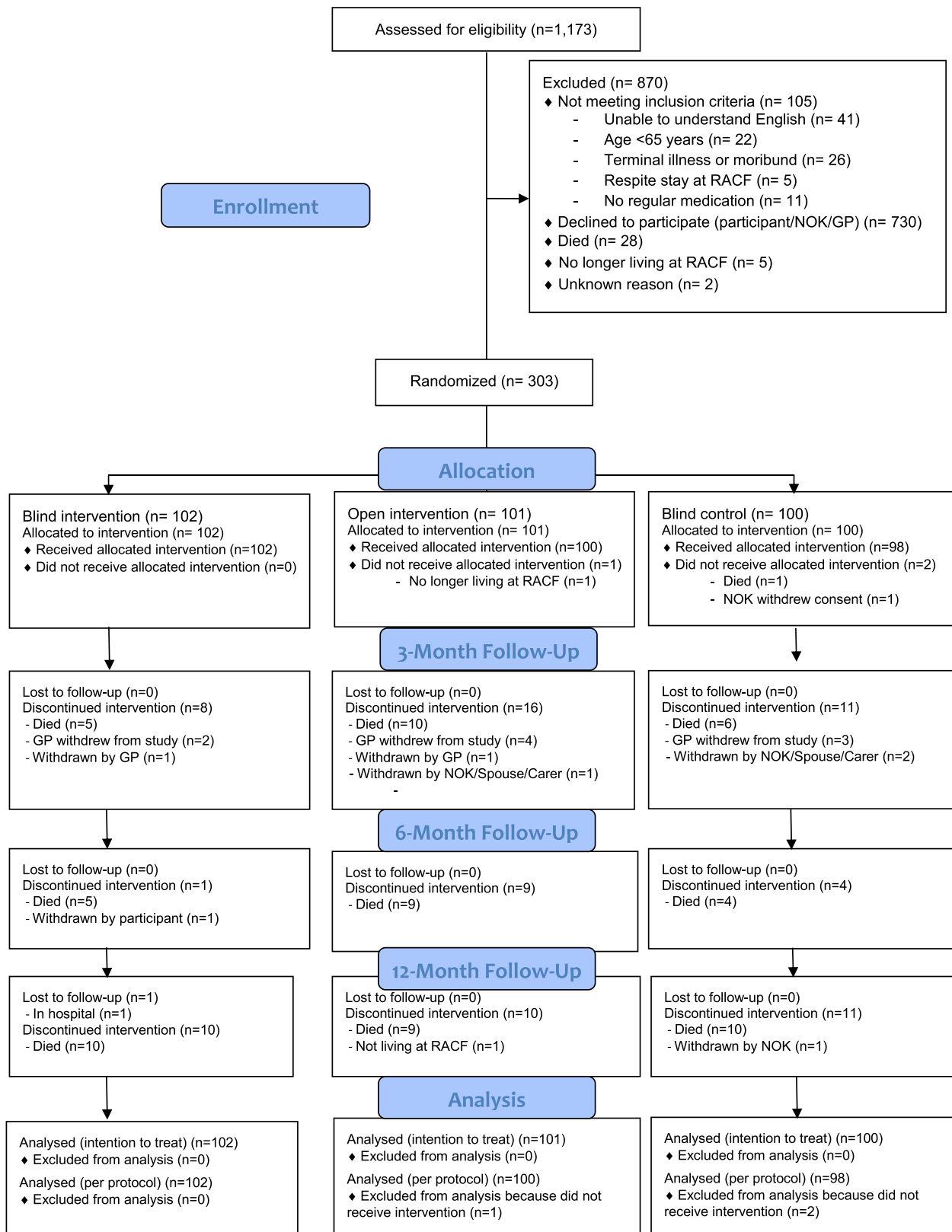
Participants were reviewed by research staff for potential ADWEs 1 week after each medication adjustment using clinical notes, patient, staff and family informants. If symptoms were stable and no potential ADWEs were reported, then implementation of the medication withdrawal plan continued as planned. In the case of suspected ADWE or another problem (such as inter-current illness), alternatives were to (i) restart the target medicine, (ii) delay the withdrawal plan (i.e. delay the next scheduled change for a fortnight) or (iii) cease the withdrawal plan (i.e. continue with a tapered dose but forego further dose reductions). Recommencement of medication, and other changes to the withdrawal plan, were based on an order obtained through liaison between the study pharmacist and the GP (or, when available, facility nurse practitioner). Any additional prescribing changes by GPs were recorded.

Outcomes

Participants were followed for 12 months post-randomisation or until death, whichever was sooner. The primary outcome was the survival of participants at 12 months post-randomisation. Outcomes were assessed at 3, 6 and 12 months post-randomisation. Clinically relevant endpoints of hospital admissions (measured by self-report and RACF notes audit), falls (assessed by self-report, incident reports and RACF notes audit) and fractures (with X-ray confirmation; and in the case of vertebral fractures, a corresponding clinical history, assessed by self-report, incident reports and RACF records audit) were counted. Medication appropriateness was considered using the anticholinergic and sedative drug exposure calculated using the Drug Burden Index [20], number of potentially inappropriate medicines based on published criteria [21], and the number of regular and PRN prescription medicines. Baseline assessments repeated as outcome measures were quality of life, independence in activities of daily living, cognitive function, behavioural and psychological symptoms of dementia, and frailty.

Sample size and analysis

The *a priori* sample size calculation was based on mortality and sought to determine that the intervention did not cause harm (i.e. no significant reduction in survival). In total, 954 participants (three groups of 318) would be required to confirm mortality is not significantly increased ($\geq 9\%$) in



Downloaded from https://academic.oup.com/ageing/article/52/5/afad081/7181253 by guest on 01 June 2023

Figure 1. Participant flow diagram.

the intervention groups (compared to the control group) with 80% power at the 0.05 level of significance. Data were analysed on an intention-to-treat basis, comparing the intervention groups with the control group. There was a

pre-specified secondary ‘per protocol’ analysis with individuals who had a medication withdrawal plan implemented with at least one medicine successfully withdrawn. We compared survival according to treatment group using Cox

Table 1. Baseline clinical characteristics and medicines data

| | Blind intervention <i>n</i> = 102 | Open intervention <i>n</i> = 101 | Blind control <i>n</i> = 100 |
|---|-----------------------------------|----------------------------------|------------------------------|
| Gender (male, <i>n</i> , %) | 25 (24%) | 25 (25%) | 23 (23%) |
| Age, years | 85.8 ± 7.1 | 84.8 ± 7.7 | 85. ± 7.2 |
| Weight (kg) | 66 ± 17 | 67 ± 17 | 67 ± 19 |
| Body mass index | 25.3 ± 5.4 | 25.8 ± 6.4 | 25.7 ± 6.5 |
| BP systolic (seated, mmHg) | 128 ± 21 | 134 ± 22 | 131 ± 22 |
| BP diastolic (seated, mmHg) | 75 ± 10 | 77 ± 12 | 75 ± 11 |
| Heart rate (seated or lying, b.p.m.) | 77 ± 11 | 74 ± 11 | 75 ± 13 |
| Faecal incontinence in last 2 weeks (<i>n</i> , %) | 49 (48.5%) | 39 (39.6%) | 44 (44.4%) |
| Charlson's Weighted Index of Comorbidity | 1.3 ± 0.5 | 1.4 ± 0.6 | 1.3 ± 0.5 |
| Frailty Index | 0.31 ± 0.08 | 0.32 ± 0.08 | 0.31 ± 0.09 |
| Medication side effects—frequency (mean score; not during past month [score of zero], less than once per week [score of 1], once or more per week [score of 2], daily or almost daily [score of 3]) | 2.3 ± 3.7 | 2.9 ± 4.6 | 2.4 ± 4.2 |
| Medication side effects—severity (mean score; causing no [score of zero], mild [score of 1], moderate [score of 2] or severe [score of 3] distress) | 1.4 ± 2.9 | 1.9 ± 3.6 | 1.5 ± 2.9 |
| Modified Barthel Index | 45 ± 30 | 50 ± 34 | 47 ± 33 |
| Mini-Mental Examination Score | 14.2 ± 9.9 | 16.1 ± 10.9 | 15.3 ± 10.0 |
| Quality of life EQ-5D-5L, staff informant [14] | 0.58 ± 0.27 | 0.61 ± 0.30 | 0.62 ± 0.26 |
| Quality of life EQ-5D-5L, self-reported [14] | 0.73 ± 0.26 | 0.78 ± 0.20 | 0.63 ± 0.26 |
| 10-Item NPI [13] | 16.8 ± 18.9 | 13.7 ± 17.6 | 9.7 ± 10.2 |
| 12-Item NPI [13] | 19.8 ± 22.1 | 15.5 ± 19.1 | 11.6 ± 11.8 |
| 10-Item NPI Distress [13] | 6.7 ± 7.6 | 5.4 ± 6.3 | 4.3 ± 4.5 |
| 12-Item NPI Distress [13] | 7.9 ± 8.9 | 6.1 ± 7.0 | 4.9 ± 5.1 |
| Beliefs about medicines [16] | | | |
| <i>Specific concerns</i> | 17.3 ± 4.7 | 17.7 ± 3.5 | 18.1 ± 4.0 |
| <i>Specific necessity</i> | 12.6 ± 4.2 | 14.2 ± 3.8 | 13.2 ± 5.2 |
| <i>General overuse</i> | 12.0 ± 3.5 | 11.9 ± 3.2 | 13.0 ± 3.1 |
| <i>General harm</i> | 13.4 ± 2.9 | 14.3 ± 3.1 | 14.7 ± 2.8 |
| Regular medicines, total (all ingredients) | 10.1 ± 4.4 | 10.7 ± 4.4 | 10.1 ± 4.8 |
| Regular medicines, solid oral dose forms (potential targets) | 7.6 ± 3.4 | 8.1 ± 3.8 | 7.7 ± 3.7 |
| PRN medicines | | | |
| PRN charted | 3.9 ± 2.7 | 3.5 ± 2.4 | 3.6 ± 2.6 |
| PRN administered at least once, WA only | 1.1 ± 1.3 | 0.6 ± 0.8 | 0.9 ± 1.6 |

Data are mean ± unless otherwise specified

proportional hazards regression. A pre-specified secondary analysis adjusting for baseline variables (e.g. age) was also conducted. Categorical secondary outcomes (i.e. hospital admission, and fall or fracture at 12 months post-enrolment) were compared using the chi-square statistic. We compared quality of life, Drug Burden Index, modified Barthel index scores, neuropsychiatric symptoms, MMSE and Frailty Index over time (at 3, 6 months and 1 year) using two-sided *t*-tests. *P* values of less than 0.05 were considered significant.

Results

We screened 1,173 residents for eligibility between 2014 and 2018, with follow-up concluding in 2019, at 17 participating residential aged care facilities (Figure 1). Approximately one-quarter of the eligible population were enrolled, had a medication withdrawal plan developed and were randomised (*n* = 303 residing in 17 RACFs across Sydney and Perth).

Baseline data

Fewer than one-third of participants had no cognitive impairment; only 86 (28.1%) participants had an MMSE over 23. Participants used regular medicines containing an average of 10.3 ± 4.5 ingredients daily in 9.5 ± 4.1 (0, 22)

different pharmaceutical products (i.e. oral, topical, etc.). The demographic data, clinical characteristics and medicine use for each group are shown in Table 1. The medication regimens used at baseline have been described in detail previously [22].

Intervention

Blinding by over-encapsulation appeared successful as perceptions of group allocation did not vary significantly between the two blinded groups (Supplementary Table 1). There was no difference in the number of deprescribing target medicines recommended by the pharmacists or agreed to by the GP across the three groups (Supplementary Table 2). Significantly more people had at least one medicine withdrawn in the open than in the blind intervention group. There were 2.3 ± 2.2 blinded study medicines administered per participant at the 12-month follow-up in both the blind intervention (i.e. over-encapsulated reduced dose of usual medicine, or placebo) and blind control (i.e. usual medicines over-encapsulated) group, while participants in the open intervention group had 2.8 ± 2.2 medicines deprescribed. There was a highly significant reduction in the total number of medicines used per participant in both intervention

Table 2. Number of medicines used and drug burden index scores at baseline, 3, 6 and 12 months per participant

| | Number of medicines (including medicines commenced after baseline) | | | | Medicines deprescribed from baseline to 12 months | |
|---|--|------------|------------|------------|---|---------|
| | Baseline | 3 months | 6 months | 12 months | Difference (95% CI) | P value |
| Number of different medicines used, all active ingredients | | | | | | |
| Blind intervention | 10.1 ± 4.4 | 7.7 ± 3.6 | 7.5 ± 3.6 | 7.6 ± 3.9 | -2.4 (-3.2, -1.6) | <0.0001 |
| Open intervention | 10.7 ± 4.4 | 8.7 ± 4.3 | 9.1 ± 4.6 | 9.4 ± 4.5 | -1.9 (-2.7, 1.0) | <0.0001 |
| Blind control | 10.1 ± 4.8 | 10.1 ± 4.8 | 10.5 ± 4.7 | 10.4 ± 5.0 | 0.0 (-0.7, 0.8) | 0.9116 |
| Number of different medicines used, administered as solid oral doses (eligible targets for deprescribing) | | | | | | |
| Blind intervention (A) | 7.6 ± 3.4 | 5.0 ± 2.5 | 4.9 ± 2.8 | 4.9 ± 2.8 | -2.7 (-3.5, -2.0) | <0.0001 |
| Open intervention (B) | 8.1 ± 3.8 | 5.9 ± 3.4 | 6.1 ± 3.4 | 6.4 ± 3.3 | -2.3 (-3.1, -1.5) | <0.0001 |
| Blind control | 7.7 ± 3.7 | 7.7 ± 3.7 | 8.2 ± 3.6 | 7.8 ± 3.9 | -0.2 (0.9, 0.4) | 0.4637 |
| Number of medicines charted for <i>pro ne nata</i> (PRN) administration | | | | | | |
| Blind intervention | 3.9 ± 2.7 | 4.2 ± 3.0 | 4.6 ± 3.0 | 4.5 ± 3.1 | 0.7 (0.3, 1.2) | 0.0017 |
| Open intervention | 3.5 ± 2.4 | 3.4 ± 2.7 | 3.6 ± 2.8 | 3.6 ± 2.6 | 0.5 (0.1, 0.9) | 0.0084 |
| Blind control (C) | 3.6 ± 2.6 | 3.9 ± 2.8 | 4.1 ± 2.9 | 4.1 ± 2.7 | 0.8 (0.4, 1.3) | 0.0010 |
| Blind intervention | 1.1 ± 1.3 | 1.2 ± 1.5 | 1.3 ± 1.5 | 1.4 ± 1.4 | 0.3 (-0.1, 0.7) | 0.1483 |
| Open intervention | 0.6 ± 0.8 | 0.6 ± 1.1 | 1.0 ± 1.2 | 0.7 ± 1.0 | 0.3 (-0.1, 0.6) | 0.1130 |
| Blind control (C) | 0.9 ± 1.6 | 1.0 ± 1.2 | 1.1 ± 1.5 | 0.9 ± 0.9 | 0.1 (-0.2, 0.4) | 0.6214 |
| Drug Burden Index score per participant | | | | | | |
| Blind intervention | 1.0 ± 0.9 | 0.9 ± 0.9 | 1.0 ± 0.8 | 1.0 ± 0.8 | 0.0 (-0.1, 0.1) | 0.9377 |
| Open intervention | 1.1 ± 0.9 | 1.0 ± 0.9 | 1.0 ± 0.8 | 1.0 ± 0.8 | -0.1 (-0.2, 0.0) | 0.1596 |
| Blind control | 1.1 ± 0.9 | 1.1 ± 0.9 | 1.1 ± 0.8 | 1.1 ± 0.9 | 0.1 (-0.0, 0.2) | 0.1396 |

Number of medicines administered at least once in preceding 4 weeks for *pro ne nata* (PRN) administration (data available for $n = 244$)

groups compared to the control group without an increase in the number of PRN medicines charted or administered or a significant change in Drug Burden Index (Table 2).

Primary outcome

Survival data are presented in Figure 2. In the 12 months from randomisation, there were 20 deaths (20%) in the blind control group with 20 deaths (20%) in the blind intervention group (HR 0.93, 95% CI 0.50, 1.73, $P = 0.83$), and 28 deaths (28%) in the open intervention group (HR 1.47, 95% CI 0.83, 2.61, $P = 0.19$). In the pre-specified per-protocol analysis, there were 17 deaths out of 66 participants (26%) in the blind control group, 12 deaths (18%) of 82 participants in the blind intervention group (HR 0.67, 95% CI 0.32, 1.40, $P = 0.29$) and 25 deaths of the 66 participants (30%) in the open intervention group (HR 1.25, 95% CI 0.68, 2.32, $P = 0.47$). The adjusted hazard ratios for the intention-to-treat and per-protocol analysis are presented in Supplementary Table 3.

Secondary outcomes

Secondary outcomes at 3, 6 and 12 months are presented in Table 3. There were no significant changes observed in quality of life, Modified Barthel Index scores, neuropsychiatric symptoms and Frailty Index at any time point.

Adverse events

Adverse events are presented in Supplementary Table 4. There were no significant differences observed in the attribution, outcome or action taken between the three groups. There were significantly more serious events in the

blind control group than either intervention group. People who experienced AEs held similar beliefs about medicines and had not reported any differences in their experience of medication side effects compared to those who did not experience AEs across all three groups (Supplementary Table 5). The report of an AE was significantly associated with a consistently greater number of regular medicines across all three groups. Impaired cognition was consistently associated with a reduced incidence of AEs across all three groups.

Discussion

Main findings

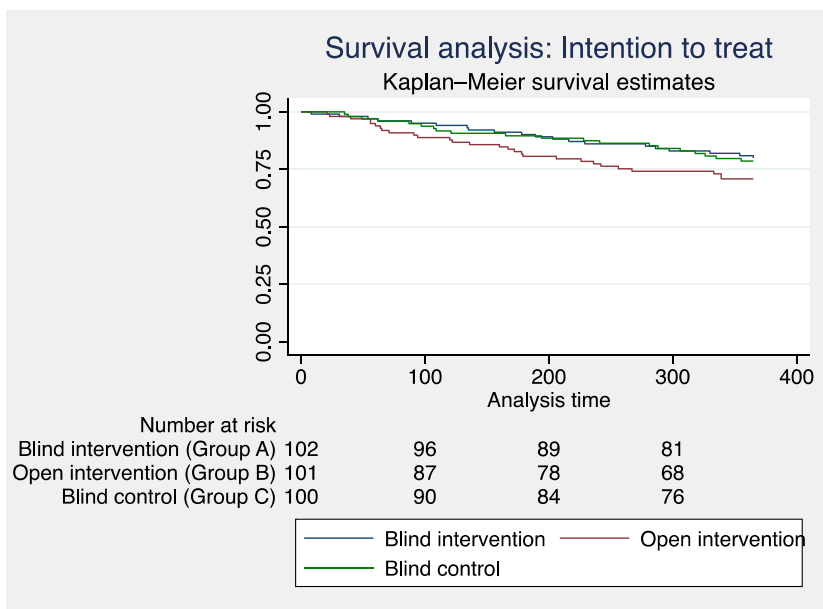
This study found that a pharmacist-led and GP-approved deprescribing intervention in aged care residents reduced number of medicines used at 12 months, without apparent adverse effects on clinical outcomes.

Significance

Reduction in medication use in residential aged care may reduce the risk of iatrogenic harms and medication errors, and nursing time involved in administering complex medication regimens. Although the field of deprescribing is rapidly advancing, very few robust studies have used blinded deprescribing interventions. As the first blinded randomised controlled trial of a deprescribing intervention designed to reduce polypharmacy through cessation of multiple different medicines in people living in residential aged care facilities, our data are an important contribution to the evidence base. Blinded data address multiple biases relevant to medication use (both positive 'placebo' effects and nocebo effects, but

Deprescribing to optimise health outcomes for frail older people

a: Kaplan Meier survival plot (intention to treat analysis)



b: Kaplan Meier survival plot (per protocol analysis)

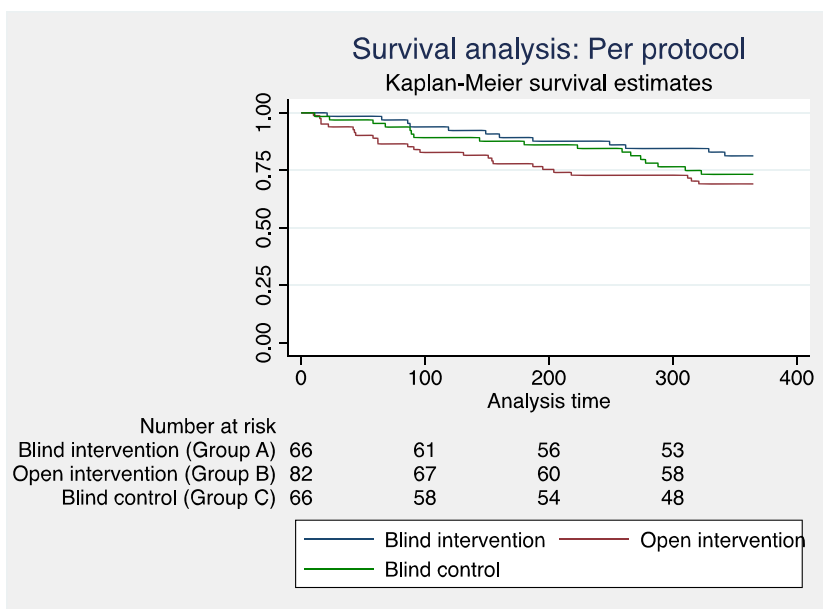


Figure 2. a: Kaplan–Meier survival plot (intention-to-treat analysis). b: Kaplan–Meier survival plot (per-protocol analysis).

also potential performance biases relevant to deprescribing). The open intervention group provides pragmatic data applicable to routine clinical practice.

Results in context

The results of this study are consistent with studies on withdrawal of individual classes of medicines suggesting that some medicines prescribed for older people living in residential aged care facilities are unnecessary [23]. Our

intervention, achieving successful withdrawal of more than two medicines per participant in the blind intervention group, had a greater impact than earlier studies achieving reductions of around one medicine per participant on average [6]. At the time our trial was designed, there was genuine equipoise with respect to deprescribing interventions in frail older people. Increasingly, the available data suggest that deprescribing is not only safe but may improve clinical outcomes in frail older people exposed to polypharmacy [6, 24, 25]. In this context, the present findings of a possible

Table 3. Secondary outcomes for open and blind intervention groups relative to control

| Group | Blind control | Open intervention | | Blind intervention | |
|---|---------------|-------------------|----------|--------------------|----------|
| | | Score | <i>P</i> | Score | <i>P</i> |
| 12 months | | | | | |
| Quality of Life EQ-5D-5L (Utilities), staff informant [15] | 0.58 ± 0.29 | 0.61 ± 0.29 | 0.57 | 0.51 ± 0.32 | 0.167 |
| Independence in ADL (Modified Barthel Index) | 43 ± 33 | 47 ± 34 | 0.49 | 34 ± 33 | 0.12 |
| Mini-Mental Examination Score | 14.2 ± 10.5 | 14.8 ± 10.5 | 0.75 | 9.8 ± 10.2 | 0.01 |
| 10-Item Neuro-Psychiatric Inventory (NPI) [13] | 13.1 ± 16.8 | 13.9 ± 16.8 | 0.54 | 15.1 ± 15.9 | 0.47 |
| 12-Item NPI [13] | 15.3 ± 18.4 | 16.1 ± 20.5 | 0.82 | 17.1 ± 17.3 | 0.54 |
| 10-Item NPI Distress [13] | 4.9 ± 5.9 | 5.1 ± 5.8 | 0.80 | 5.8 ± 6.2 | 0.34 |
| 12-Item NPI Distress [13] | 5.6 ± 6.6 | 5.9 ± 7.2 | 0.83 | 6.6 ± 6.8 | 0.36 |
| Frailty | 0.32 ± 0.10 | 0.33 ± 0.07 | 0.74 | 0.33 ± 0.10 | 0.52 |
| Medication side effects, frequency | 1.9 ± 3.1 | 1.6 ± 3.4 | 0.45 | 1.5 ± 2.9 | 0.58 |
| Medication side effects, severity | 1.2 ± 2.4 | 1.1 ± 2.7 | 0.88 | 0.9 ± 1.9 | 0.38 |
| Hospital admissions per resident, median (IQR) | 0 (1) | 0 (1) | – | 0 (1) | – |
| Falls per resident | 0 (2) | 0 (2) | – | 0 (2) | – |
| Fractures per resident, <i>n</i> (%) | 12 (12%) | 9 (9%) | – | 6 (6%) | – |
| 6 months | | | | | |
| Quality of Life EQ-5D-5L (Utilities), staff informant [15] | 0.55 ± 0.27 | 0.63 ± 0.30 | 0.08 | 0.55 ± 0.26 | 0.906 |
| Independence in ADL (MBI) | 41 ± 32 | 47 ± 32 | 0.20 | 40 ± 33 | 0.83 |
| Mini-Mental Examination Score | 14.0 ± 11.0 | 14.5 ± 11.4 | 0.80 | 12.2 ± 10.5 | 0.27 |
| 10-Item NPI [13] | 12.4 ± 13.9 | 12.1 ± 14.7 | 0.88 | 14.7 ± 17.4 | 0.34 |
| 12-Item NPI [13] | 15.0 ± 16.0 | 14.3 ± 16.9 | 0.79 | 17.1 ± 19.0 | 0.43 |
| 10-Item NPI Distress [13] | 5.3 ± 5.8 | 5.0 ± 6.2 | 0.78 | 5.9 ± 6.8 | 0.52 |
| 12-Item NPI Distress [13] | 6.2 ± 6.5 | 5.9 ± 7.1 | 0.74 | 6.8 ± 7.6 | 0.61 |
| Frailty | 0.32 ± 0.09 | 0.32 ± 0.08 | 0.96 | 0.33 ± 0.09 | 0.48 |
| Medication side effects, frequency (mean score) | 1.5 ± 2.6 | 2.0 ± 3.7 | 0.69 | 1.7 ± 3.5 | 0.40 |
| Medication side effects, severity (mean score) | 1.1 ± 2.1 | 1.4 ± 3.0 | 0.49 | 1.2 ± 2.9 | 0.92 |
| 3 months | | | | | |
| Quality of Life EQ-5D-5L utility scores, staff informant [15] | 0.61 ± 0.30 | 0.64 ± 0.27 | 0.39 | 0.55 ± 0.31 | 0.25 |
| Independence in ADL (MBI) | 47 ± 33 | 49 ± 33 | 0.73 | 42 ± 32 | 0.28 |
| Mini-Mental Examination Score | 13.9 ± 11.1 | 14.9 ± 10.8 | 0.55 | 13.6 ± 10.3 | 0.85 |
| 10-Item NPI [13] | 10.7 ± 14.5 | 13.1 ± 17.2 | 0.33 | 15.0 ± 16.2 | 0.07 |
| 12-Item NPI [13] | 12.8 ± 18.5 | 15.8 ± 19.6 | 0.29 | 17.8 ± 18.6 | 0.07 |
| 10-Item NPI Distress [13] | 4.3 ± 6.0 | 5.1 ± 6.6 | 0.43 | 6.1 ± 6.8 | 0.07 |
| 12-Item NPI Distress [13] | 5.1 ± 6.9 | 6.2 ± 7.6 | 0.36 | 7.1 ± 7.6 | 0.08 |
| Frailty | 0.31 ± 0.10 | 0.31 ± 0.08 | 0.77 | 0.32 ± 0.09 | 0.22 |
| Medication side effects, frequency | 2.1 ± 3.4 | 1.9 ± 3.5 | 0.72 | 2.1 ± 3.5 | 0.92 |
| Medication side effects, severity | 1.3 ± 2.8 | 1.3 ± 2.6 | 0.98 | 1.4 ± 2.8 | 0.72 |

Data are mean ± unless otherwise specified

trend to worse survival in the open intervention group was not anticipated. The possibility of performance bias (because practitioners may alter other aspects of care when they are aware of open deprescribing), or participant biases, remains. However, although the potential harms of deprescribing (such as adverse drug withdrawal effects and recurrence of treated conditions) are well documented [26], the blinded data are reassuring with respect to the short-term adverse effects associated with deprescribing [27]. In particular, adverse effects overall largely appeared similar, and we note that adverse events were recorded more commonly in the blind control group.

Strengths and limitations

Strengths of our study are the randomised and blinded study design and clinically relevant outcomes. In addition to participants being blinded, researchers remained blind until analyses were complete, reducing the potential

for any biases to impact conduct of the study. Over-encapsulation was an imperfect form of blinding (as opposed to manufacturing identical placebo products), but it was the only method of blinding feasible for this study as multiple different medicines were targeted for deprescribing. Over-encapsulation appeared to be an adequate method of blinding in this population as group allocation remained unknown at the conclusion of the study. This may be because residential care recipients are usually administered medications by a staff member. The greatest limitation of this study is that we were unable to reach our pre-specified recruitment targets despite continued efforts to recruit RACF, GPs and residents during the study period within the available study resources. This limitation means we cannot exclude a significant impact of deprescribing on survival. Our participants may not be representative of all older people living in RACFs, given that we only recruited one-quarter of eligible participants, and our findings are unlikely to be generalisable to more robust

community-dwelling participants. This recruitment rate is lower than that observed in non-pharmacologic intervention trials in RACF [28], possibly reflecting participants' concerns about complexity of (i) the study interventions (and potential changes to their medicines), and (ii) the study design (that required RACF, individual residents, GPs and pharmacies all to agree to study participation).

Conclusions

Deprescribing of medicines for people living in residential aged care is achievable as part of a routine workflow, reduces medication exposure and does not appear to cause substantial harms. The impact of deprescribing on survival remains undetermined.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Acknowledgements: The authors acknowledge the generous support of the residents and family members as well as the RACFs, GPs and pharmacists who participated in this study. AP was supported by a University Postgraduate Award during the study. The authors acknowledge the study staff (Jenny Tasker, Leanne Kearney, Marnee Eames, Sarita Lo, Terry Jin, Rachael Kelly, Kerri Schoenauer, Ash Osborne, Georgie Lee and Melissa Casey) and assistance of Alice Tran. The authors gratefully acknowledge the contribution of study investigators David Le Couteur and the late Dr Kieran McCaul.

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: This work was supported by the National Health and Medical Research Council (GNT1045662). The funder played no role in the design, execution, analysis and interpretation of data, or writing of the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author on request.

References

1. Page AT, Falster MO, Litchfield M, Pearson SA, Etherton-Beer C. Polypharmacy among older Australians, 2006–2017: a population-based study. *Med J Aust* 2019; 211: 71–5.
2. Reeve E, Gnjjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. *British Journal of Clinical Pharmacology [Research Support, Non-US Gov't]* 2015; 80: 1254–68.
3. Graves TMDMHS, Hanlon JTPMS, Schmader KEMD *et al.* Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med* 1997; 157: 2205–10.
4. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Isr Med Assoc J* 2007; 9: 430–4.
5. Boockvar K, Fishman E, Kyriacou CK, Monias A, Gavi S, Cortes T. Adverse events due to discontinuations in drug use and dose changes in patients transferred between acute and long-term care facilities. *Arch Intern Med* 2004; 164: 545–50.
6. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2016; 82: 583–623.
7. Kua CH, Mak VSL, Huey Lee SW. Health outcomes of deprescribing interventions among older residents in nursing homes: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2019; 20: 362–372.e11.
8. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in frail older people: a randomised controlled trial. *PLoS One* 2016; 11: e0149984. <https://doi.org/10.1371/journal.pone.0149984>.
9. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 1999; 47: 850–3.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
11. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel index for stroke rehabilitation. *J Clin Epidemiol* 1989; 42: 703–9.
12. Rockwood K, Mogilner A, Mitnitski A. Changes with age in the distribution of a frailty index. *Mech Ageing Dev* 2004; 125: 517–9.
13. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44: 2308–14.
14. Herdman M, Gudex C, Lloyd A *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; 20: 1727–36.
15. Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. *Med Care* 2007; 45: 259–63.
16. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health* 1999; 14: 1–24.
17. Quek HW, Etherton-Beer C, Page A *et al.* Deprescribing for older people living in residential aged care facilities: pharmacist recommendations, doctor acceptance and implementation. *Arch Gerontol Geriatr* 2023; 107: 104910. <https://doi.org/10.1016/j.archger.2022.104910>.
18. Page AT, Potter K, Clifford R, Etherton-Beer C. Deprescribing in older people. *Maturitas* 2016; 91: 115–34.
19. Page AT, Etherton-Beer CD, Clifford RM, Burrows S, Eames M, Potter K. Deprescribing in frail older people—do doctors and pharmacists agree? *Res Social Adm Pharm* 2016; 12: 438–49.

C. Etherton-Beer *et al.*

20. Hilmer SN, Mager DE, Simonsick EM *et al.* A drug burden index to define the functional burden of medications in older people. *Arch Intern Med* 2007; 167: 781–7.
21. Somers M, Rose E, Simmonds D, Whitelaw C, Calver J, Beer C. Quality use of medicines in residential aged care. *Aust Fam Physician* 2010; 39: 413–6.
22. Page AT, Potter K, Naganathan V *et al.* Polypharmacy and medicine regimens in older adults in residential aged care. *Arch Gerontol Geriatr* 2023; 105: 104849. <https://doi.org/10.1016/j.archger.2022.104849>.
23. Sheppard JP, Burt J, Lown M *et al.* Effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients with hypertension aged 80 years and older: the OPTIMISE randomized clinical trial. *JAMA* 2020; 323: 2039–51.
24. Kua CH, Yeo CYY, Tan PC *et al.* Association of deprescribing with reduction in mortality and hospitalization: a pragmatic stepped-wedge cluster-randomized controlled trial. *J Am Med Dir Assoc* 2021; 22: 82–89.e3.
25. Wu H, Kouladjian O'Donnell L, Fujita K, Masnoon N, Hilmer SN. Deprescribing in the older patient: a narrative review of challenges and solutions. *Int J Gen Med* 2021; 14: 3793–807.
26. Rea F, Biffi A, Ronco R *et al.* Cardiovascular outcomes and mortality associated with discontinuing statins in older patients receiving polypharmacy. *JAMA Netw Open* 2021; 4: e2113186. <https://doi.org/10.1001/jamanetworkopen.2021.13186>.
27. Reeve E, Moriarty F, Nahas R, Turner JP, Kouladjian O'Donnell L, Hilmer SN. A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf* 2018; 17: 39–49.
28. Beer C, Horner B, Flicker L *et al.* A cluster-randomised trial of staff education to improve the quality of life of people with dementia living in residential care: the DIRECT study. *PloS One*[Research Support, Non-U.S. Gov't] 2011; 6: e28155. <https://doi.org/10.1371/journal.pone.0028155>.

Received 15 November 2022; editorial decision 24 March 2023