Title: Common combinations of medications used among oldest old women: a population-based study over 15 years

Kaeshaelya Thiruchelvam [1,2 *], Julie Byles [1,3], Syed Shahzad Hasan [1,4], Nicholas Egan [1,3], Dominic Cavenagh [1,3], Therese Kairuz [1,2]

[1] University of Newcastle, University Drive, Callaghan, New South Wales 2308, Australia

[2] International Medical University, 126 Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

[3] Priority Research Centre for Generational Health and Ageing, Hunter Medical Research Institute, New Lambton Heights, New South Wales 2305, Australia

[4] University of Huddersfield, Queensgate, Huddersfield HD1 3DH, United Kingdom

- Ms Kaeshaelya Thiruchelvam * **(Corresponding author)**
  ORCID ID: https://orcid.org/0000-0002-3754-1690
  kaeshaelyathiruchelvam@uon.edu.au; kaeshaelya@gmail.com
  Mobile num: +61409622678 (Australia)

- Professor Julie Byles
  ORCID ID: https://orcid.org/0000-0002-3984-6877

- Dr Syed Shahzad Hasan
  ORCID ID: https://orcid.org/0000-0002-4058-2215

- Mr Nicholas Egan
  ORCID ID: https://orcid.org/0000-0002-0854-7444

- Mr Dominic Cavenagh
  ORCID ID: https://orcid.org/0000-0002-9241-5056

- Associate Professor Therese Kairuz

  ORCID ID: https://orcid.org/0000-0002-3311-187X

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Abstract

Background: Older people use many medications, but combinations of medications used among the oldest old (≥80 years) are not commonly reported.

Aims: This study aimed to determine common combinations of medications used among women aged 77 to 96 years, and to describe characteristics associated with these combinations.

Methods: A cohort study of older women enrolled in the Australian Longitudinal Study on Women's Health over a 15-year period was used to determine combinations of medications used using latent class analysis. Multinomial logistic regression was used to determine characteristics associated with these combinations.

Results: Highest medication users during the study were for the cardiovascular (2003: 80.28%; 2017: 85.63%) and nervous (2003: 66.03%; 2017: 75.41%) systems. A 3-class latent model described medication use combinations; Class 1: 'Cardiovascular & neurology anatomical group' (27.25%) included participants using medications of the cardiovascular and nervous systems in their later years, Class 2: 'Multiple anatomical group' (16.49%), and Class 3: 'Antiinfectives & multiple anatomical group' (56.27%). When compared to the reference class (Class 1), the risk of participants being in Class 3 was slightly higher than being in Class 2 if they had >4 general practitioner visits (RRR 2.37; 95% CI: 2.08, 2.71), Department of Veterans Affairs' coverage (RRR 1.59; 95% CI: 1.36, 1.86), ≥4 chronic diseases (RRR 3.16; 95% CI: 2.56, 3.90) and were frail (RRR 1.47; 95% CI: 1.27, 1.69).

Conclusion: Identification of combinations of medication use may provide opportunities to develop multimorbidity guidelines and target medication reviews, and may help reduce medication load for older individuals.

Keywords: Aging, older people, medication combinations, medication pattern, medication use

Introduction

Globally, the number of older people are increasing and constitute a growing share of the population in almost every country with implications in all sectors of society, particularly healthcare. People aged 80 years or older are an important group within the aging population, commonly referred to as the 'oldest old' [1]. Globally in 2017, women represented the majority (61%) of this oldest age group [1], and women have been reported to live longer than men [2]. In Australia, 13% of the population are aged 85 years and over, and women comprise 63% of this age group [3].

Older age is associated with multiple chronic diseases and multimorbidity. Multimorbidity is commonly defined as the co-occurrence of two or more health conditions and is prevalent in the older population, who predominantly have non-communicable diseases [4]. This effect can lead to concomitant use of multiple medications, due to implementation of disease-specific guidelines which recommend multiple medications to manage each condition, and accumulation of medications across multiple medications. Due to pharmacokinetic and pharmacodynamic changes in the oldest old, inappropriate prescribing, and medication non-adherence, multiple medication use in older people is associated with increased adverse drug events and risk of drug interactions. Adverse outcomes can include falls, functional decline, hospitalisations and mortality [5], and with an associated increase in healthcare costs [6].

Evaluation of medication use among oldest old women is essential to minimise unnecessary medication burden, identify medication needs for optimal health, and ensure sufficient supply and medication management for this population. Most literature on medication use is usually disease-centric [7] and focuses on determining medication use at the prescription level [8], i.e number of medications as opposed to number of individuals using medications. Whilst it is useful to determine the prevalence of polypharmacy which is based on number of medications [7, 9-11], it is also important to identify different types of medications used in combination, so that future interventions can focus on groups of medications for comorbid conditions, and considering potential interactions. This study aims to use latent class analysis (LCA) to identify latent groups of women based on a set of observed characteristics. Although it is widely known that use of multiple medications is common among older people, there have been no other studies that used this method to identify common

combinations of medications that will aid in development of multimorbidity guidelines for older people, which is severely lacking. Given the growing proportion of oldest old women, the objectives of this study were to determine common combinations of medications used in this population, and describe variables associated with these combinations.

Methods

Study design and data source

Participants in this study were from the 1921-1926 cohort of the Australian Longitudinal Study on Women's Health (ALSWH) [12], an ongoing longitudinal population-based survey that determines the health and wellbeing of Australian women. Participants from the ALSWH were randomly selected from the Australian Medicare database, a scheme that provides Australian residents with various healthcare services [13]. Participants were first surveyed in 1996 (Survey 1: age 70-75 years; *n*=12432) with 3-yearly follow-up surveys in 1999 (Survey 2: age 73-78 years; *n*=10434), 2002 (Survey 3: age 76-81 years; *n*=8647), 2005 (Survey 4: age 79-84 years; *n*=7158), 2008 (Survey 5: age 82-87 years; *n*=5561), and 2011 (Survey 6: age 85-90 years; *n*=4055), and 6-monthly surveys thereafter [12].

Survey data were linked to data from the Pharmaceutical Benefits Scheme (PBS), an Australian government program which provides access to subsidised prescription medications for permanent residents [14]. Although PBS data were made available from June 2002, PBS data was complete for all participants in 2003 and include the Repatriation PBS data, which is a further beneficiary scheme of a small cohort of about 250,000 people who are war widows/widowers, veterans or their dependents; the Repartriation PBS data is subsidised by the Department of Veterans Affairs (DVA) [15].

Eligible participants and study time points

ALSWH participants were eligible to be included in the analyses if they:

i) Remained alive at 1 January 2003, and

ii) Had a PBS record in 2003, and

iii) Had not withdrawn consent to data linkage with the PBS data prior to 2017

Participants were excluded if they did not meet the eligibility criteria and, despite being eligible for PBS data linkage, if they did not have any PBS records.

All analyses were conducted among participants who remained alive at each year. The first part of the study was descriptive and included two analyses; the first determined medication use from 2003 (age 77-82 years) to 2017 (age 91-96 years), and the second was cross-sectional at 2011 (age 85-90 years). The second part of the study was also cross-sectional and determined common combinations of medications and variables associated with these combinations in 2011 among participants aged 85 to 90 years through latent class analysis (LCA). A flowchart of participants included in the analyses are present in Online Resource 1.

Assessment of medication use

Medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [16]. The first part of the descriptive analyses included broad 'anatomical group' (ATC level 1) such as cardiovascular and nervous systems whereas the second part determined common medications based on all ATC levels. Participants were defined as using a medication in an ATC anatomical group in each year, if they had one or more prescriptions for a medication in that group for that year; proportions of participants using each ATC level were determined from a denominator which only included participants with PBS records and alive at each year. Records for 'all other non-therapeutic products' (V07A) were excluded.

Explanatory variables

Variables associated with combinations of medication use were determined *a priori* for the LCA analysis. ALSWH Survey 3 in 2002 was used to determine participants' baseline variables and Survey

6 in 2011 was used to determine variables associated with latent class membership; missing data was carried forward from preceding surveys where necessary. These variables included whether they lived alone; number of general practitioner (GP) visits in the last 12 months (≤4 times and >4 times); whether they had Department of Veterans Affairs (DVA) coverage; number of chronic diseases (0-1, 2-3, and ≥4); whether they had a fall in the previous 12 months; and frailty status (non-frail and frail) [17]. Frailty was determined using the method proposed by Lopez et al. for ALSWH participants, i.e. the FRAIL scale [17]. Education level was obtained from Survey 1 and categorised as: below Year 12, and Year 12 and above. Once diagnosed at any survey, chronic diseases were considered enduring and included hypertension, diabetes, heart disease, cancer, osteoporosis, respiratory disease, stroke, arthritis, and mental illnesses which include Alzheimer's disease/dementia, depression and anxiety or nervous disorders. Additionally, a comparison of the proportion of study participants who self-reported chronic diseases was performed according to latent class membership.

Statistical analyses

Data were analysed using Stata® IC version 16 with a significance level of 0.05. Latent class analysis (LCA) was used to classify participants with similar medication use combinations. LCA provides a classification of cases with categorical indicators [18], and in this study, participants were categorised based on level 1 ATC medication prevalence ≥10.00% at age 85-90 years. LCA models were developed sequentially from a 2-class model to a 10-class model. Relative model fit was based on parsimony and comparison of information criteria associated with each model under consideration [19]; the model with the lowest Bayesian Information Criteria (BIC) score was selected because the estimated model was non-nested [20]. The naming of the latent classes was based on conditional item response probabilities >0.5 to facilitate interpretation [19]. Multinomial logistic regression was performed to estimate the association between explanatory variables and latent class membership in a multivariable model, after performing univariate multinomial logistic regressions for each variable. Effect estimates were presented as relative risk ratios (RRR) with 95% confidence intervals (95% CI).

Ethics approval

The ALSWH has ongoing ethical approval from the Human Research Ethics Committees (HRECs) of the Universities of Newcastle and Queensland for its survey program (reference H-076-0795 and 2004000224, respectively) and for health record linkage (reference H-2011-0371 and 2012000132). In addition, access to national data collections is approved by the Australian Institute of Health and Welfare HREC (reference EC2012/1/12).

Results

Medication use for participants aged 77-96 years

A total of 10,334 participants were included in the first part of the descriptive analyses at baseline and their variables are presented in Table 1. Level 1 ATC medications used each year are listed in Online Resource 2 and summarised in Fig.1. At baseline, the proportion of participants was highest for those who used medications from the cardiovascular system (80.28%) followed by the nervous system (66.03%), alimentary tract and metabolism (62.83%), antiinfectives for systemic use (59.99%) and musculoskeletal system (53.56%). When participants were aged 80 to 85 years, the proportion of participants with the fifth highest medication use was blood and blood-forming organs (48.46%) which replaced musculoskeletal system (46.64%). This trend remained similar until participants were aged 91 to 96 years in 2017 where medications of the cardiovascular (85.63%) and nervous systems (75.41%), and antiinfectives (66.92%) were still commonly used. Medication use was also compared within each level 1 ATC over time. The largest change in the proportion of participants for medication use in 2017 compared to 2003 was for the musculoskeletal system (-17.51%), followed by the alimentary tract and metabolism (+11.31%) and nervous system (+9.38%).

Combinations of medications

The second part of the descriptive analyses included 6933 participants when aged 85-90 years, and their medication use is presented in Table 2. Agents acting on the renin-angiotensin system (61.62%), lipid modifying agents (46.42%), analgesics (63.68%), drugs for acid related disorders (51.18%),

antibacterials for systemic use (63.93%) and antithrombotic agents (49.60%) were highly used. At the medication level, paracetamol (55.91%) had the highest use, followed by aspirin (25.62%).

On LCA, the 3-class latent model was selected because it had the lowest BIC score of 2102.21 and was more interpretable compared to other classes (Online Resource 3). The 3-class latent model also had sufficient sample size in all classes, with approximately 1143 (16.49%) participants in the smallest class [19]. Fig. 2 depicts the latent class membership and estimated probabilities for level 1 ATC categories. The largest class (Class 3) comprised 3901 (56.27%) of the participants and included participants who had high conditional probability of using medications from most level 1 ATC including antiinfectives, thus named 'Antiinfectives & multiple anatomical group'. Class 2 comprised 1143 (16.49%) of the participants with high use of most anatomical groups except antiinfectives, and was named 'Multiple anatomical group'. Class 1 comprised 1889 (27.25%) of the participants with high probabilities of medication use from the cardiovascular and nervous systems, thus named 'Cardiovascular & neurology anatomical group', and formed the reference class for the regressions. Item response probabilities for each class are presented in Online Resource 4.

Variables associated with class membership

From the multivariable model (see Table 3), different groups of variables were seen to be associated with membership in Class 2 (Multiple anatomical group) and Class 3 (Antiinfectives and multiple anatomical group) when compared to the reference group, Class 1 (cardiovascular & neurology anatomical group). The risk of participants being in Class 3 was higher compared to Class 1 if they had >4 GP visits (RRR 2.37; 95% CI: 2.08, 2.71), DVA coverage (RRR 1.59; 95% CI: 1.36, 1.86), 2-3 chronic diseases (RRR 1.36; 95% CI: 1.11, 1.67), ≥4 chronic diseases (RRR 3.16; 95% CI: 2.56, 3.90), or were frail (RRR 1.47; 95% CI: 1.27, 1.69); participants had lower risk of being in Class 3 compared to Class 1 if they had an education level of Year 12 and above (RRR 0.78; 95% CI: 0.68, 0.89) or if they were living alone (RRR 0.84; 95% CI: 0.74, 0.96). The risk of participants in Class 2 compared to Class 1 had the same associated variables as Class 3 with the exception of living alone and being frail. Participants had a lower risk of being in Class 2 compared to Class 1 if they had a fall

in the last 12 months (RRR 0.80; 95% CI: 0.65, 0.97). Results of the univariate multinomial logistic regressions are presented in Online Resource 5.

Online Resource 6 depicts the proportion of study participants with chronic diseases according to latent class membership. Within each latent class, the majority of participants had the following diseases: heart disease (Class 1: 67.97%, Class 2: 87.14%, Class 3: 80.77%); hypertension (Class 1: 61.94%, Class 2: 77.60%, Class 3:71.98%); and arthritis (Class 1: 54.00%, Class 2: 56.00%, Class 3: 67.11%). Additionally, cancer was present in majority of the participants in Class 3 (53.78%).

Discussion

This study is unique due to the methodology used (latent class analyses or LCA) to provide common combinations of medications used by oldest old women. The LCA resulted in a 3-class latent model: Class 1 (Cardiovascular & neurology anatomical group), Class 2 (Multiple anatomical group) and Class 3 (Antiinfectives & multiple anatomical group). There have been other studies that used the LCA to determine patterns of substance abuse [21,22], but none that determined medication use among older people. Although it is widely known that most older people have multimorbidity and likely use multiple medications, the LCA has revealed that majority of the women in this study not only used medications from multiple anatomical groups, but also used antiinfectives frequently.

Many women aged 85 to 90 years had a higher likelihood of taking medications from multiple anatomical groups if they had more than two chronic diseases, indicating the presence of multimorbidity. This is also supported by the high use of medications from various anatomical groups for all women in the study as they aged from 77 to 96 years. We also examined the prevalence of chronic diseases according to latent class membership but did not detect distinct differences between the latent classes, except for cancer which was observed in the majority of women in Class 3. This lack of difference in the prevalence of chronic diseases between latent classes could be explained by the self-report nature of the survey which may have led to under-reporting of chronic diseases. Nevertheless, this information could be useful for drug utilization reviews which support the development of multimorbidity guidelines for older people. Current disease-specific guidelines do not

consider the cumulative impact of medications for older people with multimorbidity which can cause medication burden, perhaps resulting in a prescribing cascade [23,24]. A study that aimed to determine the extent to which national guidelines address multimorbidity reported that multimorbidity and patient compliance were not consistently accounted for and that even when guideline recommendations were explicitly adhered to, patients suffered from medication burden [23]. Therefore it is important to recognise the need for patient-centered care and to treat the 'patient' instead of the 'disease'; this can be achieved by developing guidelines that consider multimorbidity [23].

As noted in Class 3 of the LCA, most women (56%) aged 85 to 90 years were taking antiinfectives along with multiple medications. This could be a cause for concern and highlights the importance in ensuring antibacterials, antivirals and other antiinfectives like antimycotics and antimycobacterials are not regularly used, unless indicated. Women in Class 3 had an increased likelihood of having more chronic diseases and being frail which may have led to decreased activity of the immune system, i.e immunosenescence, thus predisposing them to infections [25]. This highlights the complexity of medication management among the oldest old, and the possible role of frailty which may further increase this complexity. There is an important need to review their medications to ensure antibiotics and antivirals are not chronically used. It is not uncommon for older women to have increased susceptibility to urinary tract infections, pneumonia and atypical presentation of infections [26]. Older women suffering from multimorbidity and with higher risks of infections should be identified promptly so that medication reviews may be prioritised for this group as an aid for medication management.

Furthermore, as noted from the results of the regression analyses, women with more than four GP visits in the last 12 months were associated with a higher risk of using antiinfectives and medications from multiple anatomical groups, when compared to women using cardiovascular and nervous system medications. This indicates that women with multimorbidity and potential infections are already making frequent visits to doctors, providing opportunities for doctors to review their medication lists and make referrals to pharmacists for medication reviews; pharmacist-led medication reviews is an established process in most countries [27-29]. Nevertheless, caution must be taken regarding overzealous discontinuation of medications, especially as needed medications.

Approximately 27% of women aged 85 to 90 years in our study were taking at least one cardiovascular and/or nervous system medication, and the highest proportions of medication use for women as they aged from 77 to 96 years were from the cardiovascular and nervous system groups. When the prevalence of chronic diseases was compared according to latent class membership, the majority of women in all three latent classes had heart disease, hypertension and arthritis. These conditions are reflected in the pharmacotherapy prescribed for these women. Furthermore, the snapshot of medications used by women when they were 85 to 90 years reflects high use of agents acting on the Renin-Angiotensin system (62%) and to a lesser extent, and lipid modifying agents (46%), potentially as treatment for cardiovascular diseases. The Australian Burden of Disease Study 2015 reported that coronary heart disease was present in 11% of women aged 75 to 84 years and 18% of women aged 85 years and over, which was reported as a leading cause of fatal disease burden [30]. Literature depicts a bidirectional association between coronary heart disease and mental illness, and that both diseases seem to have shared etiology, including psychological, biological, behavioural and genetic mechanisms [31]. This was in line with results from this study that depicted around one-third of women aged 85 to 90 years used psycholeptics (33%) and psychoanaleptics (32%).

A snapshot of medications used by women aged 85 to 90 years also indicate a high use of analgesics, especially opioid analgesics (33%) and paracetamol (56%), which are categorised as nervous system medications. This highlights pain management among older people, which was previously reported to be undertreated [32]. Paracetamol responds well to majority of mild to moderate pain among older people, especially if it is of musculoskeletal origin, and it is important to have both renal and hepatic functions monitored occasionally. Opioid analgesics to treat chronic noncancer pain have also been more widely accepted, and are used to treat severe nociceptive pain. However, the use of stool softeners and other laxatives to prevent and manage side effects like constipation should be highlighted, and it can be noted that about 20% of women in this group were using laxatives. It is important to understand different types of pain (neuropathic or nociceptive) and ensure appropriate analgesia is provided to older people, including adjuvant medications [32].

Study limitations

The self-report nature of the ALSWH surveys may have introduced reporting bias. In determining variables associated with membership in each latent class, this study was limited by the information collected in the ALSWH surveys. Since medication use was determined as any use in a year, there may have been overestimation of point prevalence of medication use, especially in the LCA because not all women in each class may have been using these medications in all years. It was also not possible to ascertain whether changes in medication use was a result of improved treatment because medication dosage and indications were not available in the PBS dataset. The LCA was also based on cross-sectional data which may not allow generalisability of the results. There have been considerable changes in prescribing patterns for older people over the last decade in Australia and other developed and developing countries, in particular with antacids and anticholinergic medications for various indications. Therefore, our findings pertaining common combinations of medication classes based on the LCA should be considered with caution in informing current policies and practices. Future studies should aim to assess the prevalence of clinically important drug interactions within common combinations of medications. Drug interactions is an important aspect of drug utilization and may further support the development of multimorbidity guidelines.

Conclusion

The application of the LCA has shed light on the the common combinations of medications used by oldest old women. This study provides valuable information for the development of multimorbidity guidelines for older people, which should be developed around these medication constellations, while optimising medication use aspects such as reducing the potential for drug interactions and adverse drug events. High use of medications of the cardiovascular, nervous, alimentary tract, musculoskeletal and blood forming systems indicate the need to direct attention to determining the need and appropriateness of these medications among the oldest old. The frequent use of antiinfectives in this study warrants the inclusion of these agents in future studies, and attention to their concomitant use among women with other multiple conditions and those using other medications. It is important to ensure older women have their medication combinations reviewed

388 regularly to determine their appropriateness. Subsidised medication reviews are essential for our
389 oldest old women.
390
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393 The Australian Government Department of Health fund the Australian Longitudinal Study on Women's
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396
397 **Conflicts of interest**
398 The authors have no conflicts of interest that are relevant to the contents of this manuscript.
399
400 **Ethics approval**
401 The ALSWH has ongoing ethical approval from the Human Research Ethics Committees (HRECs) of
402 the Universities of Newcastle and Queensland for its survey program (reference H-076-0795 and
403 2004000224, respectively) and for health record linkage (reference H-2011-0371 and 2012000132).
404 In addition, access to national data collections is approved by the Australian Institute of Health and
405 Welfare HREC (reference EC2012/1/12).
406
407 **Availability of data and material**
408 Use of the ALSWH dataset is subject to strict ethical conditions due to the personal nature of the data
409 collected. The ethics committees that oversee the ALSWH are the Australian Government
410 Department of Health Human Research Ethics Committee and the Human Research Ethics
411 Committees at the University of Queensland and the University of Newcastle. Ethical approval of the
412 ALSWH specifies that de-identified data are only available to collaborating researchers where there is
413 a formal request to make use of the material, and that each request has to be approved by the
414 ALSWH Data Access Committee. Further details can be found at http://alswh.org.au/for-researchers
415
416 **Code availability**
417 Codes can be made available upon request.

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Authors' contributions

Kaeshaelya Thiruchelvam was involved in the concept, design, analyses, interpretation, drafting and revision of the manuscript. Julie Byles was involved in the concept, design, interpretation and revision of the manuscript. Therese Kairuz and Syed Shahzad Hasan were involved in the concept, interpretation, drafting and revision of the manuscript. Nicholas Egan and Dominic Cavenagh were involved in the design, interpretation, analyses and revision of the manuscript. All authors read and approved the final manuscript, and agree with the submission to Aging Clinical and Experimental Research. The authors are accountable for all aspects of the manuscript.

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