

Supplementary Appendix S1: Key search terms

Aged; geriatrics; aging; nursing home patient; phase 4 clinical trial; multicenter study; controlled clinical trial; clinical trial; adaptive clinical trial; community trial; intervention study; longitudinal study; postmarketing surveillance; prospective study; retrospective study; meta-analysis; case control study; observational study; cohort analysis; major clinical study; controlled study; medication compliance; drug safety; inappropriate prescribing; drug utilization review; deprescription; polypharmacy; medication therapy management; medication adherence monitoring system; medication error; pharmacoepidemiology; adverse event; adverse drug reaction; major adverse cardiac event; major adverse cardiac event; medication related problem; drug related problem; lack of drug effect; prescription drug misuse; drug dose intensification; drug dose reduction; optimal drug dose

Supplementary Appendix S2: List of journals manually searched

We performed a manual search for relevant articles from high impact journals under the categories of:

(1) General and Internal Medicine:

- New England Journal of Medicine
- Journal of the American Medical Association (JAMA Intern Med)

(2) Geriatrics and Gerontology:

- Journal of the American Medical Director Association
- Journal of Gerontology: Medical Sciences
- Age and Ageing
- Journal of the American Geriatrics Society

(3) Pharmacology and Pharmacy:

- British Journal of Clinical Pharmacology

Supplementary Appendix S3: List of 2020 articles that addressed medication use quality and safety

Articles in bold have been selected as the four top articles that have been discussed in the special article.

Medication Safety/Adverse Drug Events (ADEs)

A. Cardiovascular

1. Alqdwah-Fattouh R, Rodríguez-Martín S, de Abajo FJ, et al. Differential effects of antidepressant subgroups on risk of acute myocardial infarction: A nested case-control study. *Br J Clin Pharmacol.* 2020;**86**: 2040-2050.
2. Biffi A, Rea F, Scotti L, et al. Antidepressants and the Risk of Cardiovascular Events in Elderly Affected by Cardiovascular Disease: A Real-Life Investigation From Italy. *J Clin Psychopharmacol.* 2020;**40**: 112-121.

B. Cognitive decline/Dementia

1. Hughes D, Judge C, Murphy R, et al. Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA.* 2020;**323**: 1934-1944.
2. Dyer AH, Murphy C, Segurado R, Lawlor B, Kennelly SP. Is Ongoing Anticholinergic Burden Associated With Greater Cognitive Decline and Dementia Severity in Mild to Moderate Alzheimer's Disease? *J Gerontol A Biol Sci Med Sci.* 2020;**75**: 987-994.
3. Neelamegam M, Zgibor J, Chen H, et al. The Effect of Cumulative Anticholinergic Use on the Cognitive Function of Older Adults: Results from the Personality and

Total Health (PATH) Through Life Study. *J Gerontol A Biol Sci Med Sci.* 2020;**75**: 1706-1714.

4. Pieper NT, Grossi CM, Chan WY, et al. Anticholinergic drugs and incident dementia, mild cognitive impairment and cognitive decline: a meta-analysis. *Age Ageing.* 2020;**49**: 939-947.
5. Weigand AJ, Bondi MW, Thomas KR, et al. Association of anticholinergic medications and AD biomarkers with incidence of MCI among cognitively normal older adults. *Neurology.* 2020;**95**: e2295-e2304.

C. Falls/fractures

1. **Wei J, Lane NE, Bolster MB, et al. Association of Tramadol Use With Risk of Hip Fracture. *J Bone Miner Res.* 2020;**35**: 631-640.**
2. **Black DM, Geiger EJ, Eastell R, et al. Atypical Femur Fracture Risk versus Fragility Fracture Prevention with Bisphosphonates. *N Engl J Med.* 2020;**383**: 743-753.**
3. Lutsey PL, Norby FL, Ensrud KE, et al. Association of Anticoagulant Therapy With Risk of Fracture Among Patients With Atrial Fibrillation. *JAMA Intern Med.* 2020;**180**: 245-253.
4. Gray SL, Marcum ZA, Dublin S, et al. Association Between Medications Acting on the Central Nervous System and Fall-Related Injuries in Community-Dwelling Older Adults: A New User Cohort Study. *J Gerontol A Biol Sci Med Sci.* 2020;**75**: 1003-1009.
5. Bokrantz T, Schiöler L, Boström KB, et al. Antihypertensive drug classes and the risk of hip fracture: results from the Swedish primary care cardiovascular database. *J Hypertens.* 2020;**38**: 167-175.

6. Carrier H, Cortaredona S, Philipps V, et al. Long-term risk of hip or forearm fractures in older occasional users of benzodiazepines. *Br J Clin Pharmacol.* 2020;**86**: 2155-2164.
7. Chen YJ, Kung PT, Chou WY, Tsai WC. Alendronate medication possession ratio and the risk of second hip fracture: an 11-year population-based cohort study in Taiwan. *Osteoporos Int.* 2020;**31**: 1555-1563.
8. Ogunwale AN, Colon-Emeric CS, Sloane R, Adler RA, Lyles KW, Lee RH. Acetylcholinesterase Inhibitors Are Associated with Reduced Fracture Risk among Older Veterans with Dementia. *J Bone Miner Res.* 2020;**35**: 440-445.
9. Yoshikawa A, Ramirez G, Smith ML, et al. Opioid Use and the Risk of Falls, Fall Injuries and Fractures among Older Adults: A Systematic Review and Meta-Analysis. *J Gerontol A Biol Sci Med Sci.* 2020;**75**: 1989-1995.
10. Won DY, Byun SJ, Jeong JS, Shin JY. Association Between Acetylcholinesterase Inhibitors and Osteoporotic Fractures in Older Persons With Alzheimer's Disease. *J Am Med Dir Assoc.* 2020;**21**: 1128-1133.e1121.

D. Mortality

1. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. *JAMA.* 2020;**324**: 369-380.
2. Basciotta M, Zhou W, Ngo L, Donnino M, Marcantonio ER, Herzig SJ. Antipsychotics and the Risk of Mortality or Cardiopulmonary Arrest in Hospitalized Adults. *J Am Geriatr Soc.* 2020;**68**: 544-550.

E. Other

1. Savage RD, Visentin JD, Bronskill S, et al. Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. *JAMA Intern Med.* 2020;**180**: 643-651.
2. Hodkinson A, Tyler N, Ashcroft DM, et al. Preventable medication harm across health care settings: a systematic review and meta-analysis. *BMC Med.* 2020;**18**: 313.
3. Hill K, Sucha E, Rhodes E, et al. Risk of Hospitalization With Hemorrhage Among Older Adults Taking Clarithromycin vs Azithromycin and Direct Oral Anticoagulants. *JAMA Intern Med.* 2020;**180**: 1052-1060.
4. Nicolau JC, Bhatt DL, Hohnloser SH, et al. Dabigatran Dual Therapy vs Warfarin Triple Therapy Post-Percutaneous Coronary Intervention in Patients with Atrial Fibrillation With/Without a Proton Pump Inhibitor: A Pre-Specified Analysis of the RE-DUAL PCI Trial. *Drugs.* 2020;**80**: 995-1005.
5. Ohnuma T, Raghunathan K, Moore S, et al. Dose-Dependent Association of Gabapentinoids with Pulmonary Complications After Total Hip and Knee Arthroplasties. *J Bone Joint Surg Am.* 2020;**102**: 221-229.
6. Tapiainen V, Lavikainen P, Koponen M, et al. The Risk of Head Injuries Associated With Antipsychotic Use Among Persons With Alzheimer's disease. *J Am Geriatr Soc.* 2020;**68**: 595-602.
7. Tecklenborg S, Byrne C, Cahir C, Brown L, Bennett K. Interventions to Reduce Adverse Drug Event-Related Outcomes in Older Adults: A Systematic Review and Meta-analysis. *Drugs Aging.* 2020;**37**: 91-98.
8. Zullo AR, Ofori-Asenso R, Wood M, et al. Effects of Statins for Secondary Prevention on Functioning and Other Outcomes Among Nursing Home Residents. *J Am Med Dir Assoc.* 2020;**21**: 500-507.e508.

Deprescribing/Discontinuation

1. 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**: 2039-2051.
2. Niznik JD, Zhao X, He M, et al. Risk for Health Events After Deprescribing Acetylcholinesterase Inhibitors in Nursing Home Residents With Severe Dementia. *J Am Geriatr Soc*. 2020;**68**: 699-707.
3. Niznik JD, Hunnicutt JN, Zhao X, et al. Deintensification of Diabetes Medications among Veterans at the End of Life in VA Nursing Homes. *J Am Geriatr Soc*. 2020;**68**: 736-745.
4. Curtin D, Jennings E, Daunt R, et al. Deprescribing in Older People Approaching End of Life: A Randomized Controlled Trial Using STOPPFrail Criteria. *J Am Geriatr Soc*. 2020;**68**: 762-769.
5. Evrard P, Henrard S, Foulon V, Spinewine A. Benzodiazepine Use and Deprescribing in Belgian Nursing Homes: Results from the COME-ON Study. *J Am Geriatr Soc*. 2020;**68**: 2768-2777.
6. Niznik JD, Zhao X, He M, et al. Impact of deprescribing AChEIs on aggressive behaviors and antipsychotic prescribing. *Alzheimers Dement*. 2020;**16**: 630-640.
7. Rashid R, Chang C, Niu F, et al. Evaluation of a Pharmacist-Managed Nonsteroidal Anti-Inflammatory Drugs Deprescribing Program in an Integrated Health Care System. *J Manag Care Spec Pharm*. 2020;**26**: 918-924.
8. Springer SP, Mor MK, Sileanu F, et al. Incidence and Predictors of Aspirin Discontinuation in Older Adult Veteran Nursing Home Residents at End of Life. *J Am Geriatr Soc*. 2020;**68**: 725-735.

9. Thorpe CT, Sileanu FE, Mor MK, et al. Discontinuation of Statins in Veterans Admitted to Nursing Homes near the End of Life. *J Am Geriatr Soc.* 2020;**68**: 2609-2619.
10. Zechmann S, Senn O, Valeri F, et al. Effect of a patient-centred deprescribing procedure in older multimorbid patients in Swiss primary care - A cluster-randomised clinical trial. *BMC Geriatr.* 2020;**20**: 471.

Medication adherence

1. Fanaroff AC, Peterson ED, Kaltenbach LA, et al. Association of a P2Y12 Inhibitor Copayment Reduction Intervention With Persistence and Adherence With Other Secondary Prevention Medications: A Post Hoc Analysis of the ARTEMIS Cluster-Randomized Clinical Trial. *JAMA Cardiol.* 2020;**5**: 38-46.
2. Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. *Cochrane Database Syst Rev.* 2020;**5**: Cd012419.
3. Jackson LR, Kim S, Blanco R, et al. Discontinuation rates of warfarin versus direct acting oral anticoagulants in US clinical practice: Results from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). *Am Heart J.* 2020;**226**: 85-93.

Medication Use Trends

1. Secnik J, Xu H, Schwertner E, et al. Dementia Diagnosis Is Associated with Changes in Antidiabetic Drug Prescription: An Open-Cohort Study of ~130,000 Swedish Subjects over 14 Years. *J Alzheimers Dis.* 2020;**76**: 1581-1594.

Suboptimal Prescribing

A. PIMs/low-value medications

1. Hirdes JP, Major J, Didic S, et al. A Canadian Cohort Study to Evaluate the Outcomes Associated with a Multicenter Initiative to Reduce Antipsychotic Use in Long-Term Care Homes. *J Am Med Dir Assoc.* 2020;**21**: 817-822.
2. Weir DL, Lee TC, McDonald EG, et al. Both New and Chronic Potentially Inappropriate Medications Continued at Hospital Discharge Are Associated With Increased Risk of Adverse Events. *J Am Geriatr Soc.* 2020;**68**: 1184-1192.
3. Liew TM, Lee CS, Goh SKL, Chang ZY. The prevalence and impact of potentially inappropriate prescribing among older persons in primary care settings: multilevel meta-analysis. *Age Ageing.* 2020;**49**: 570-579.

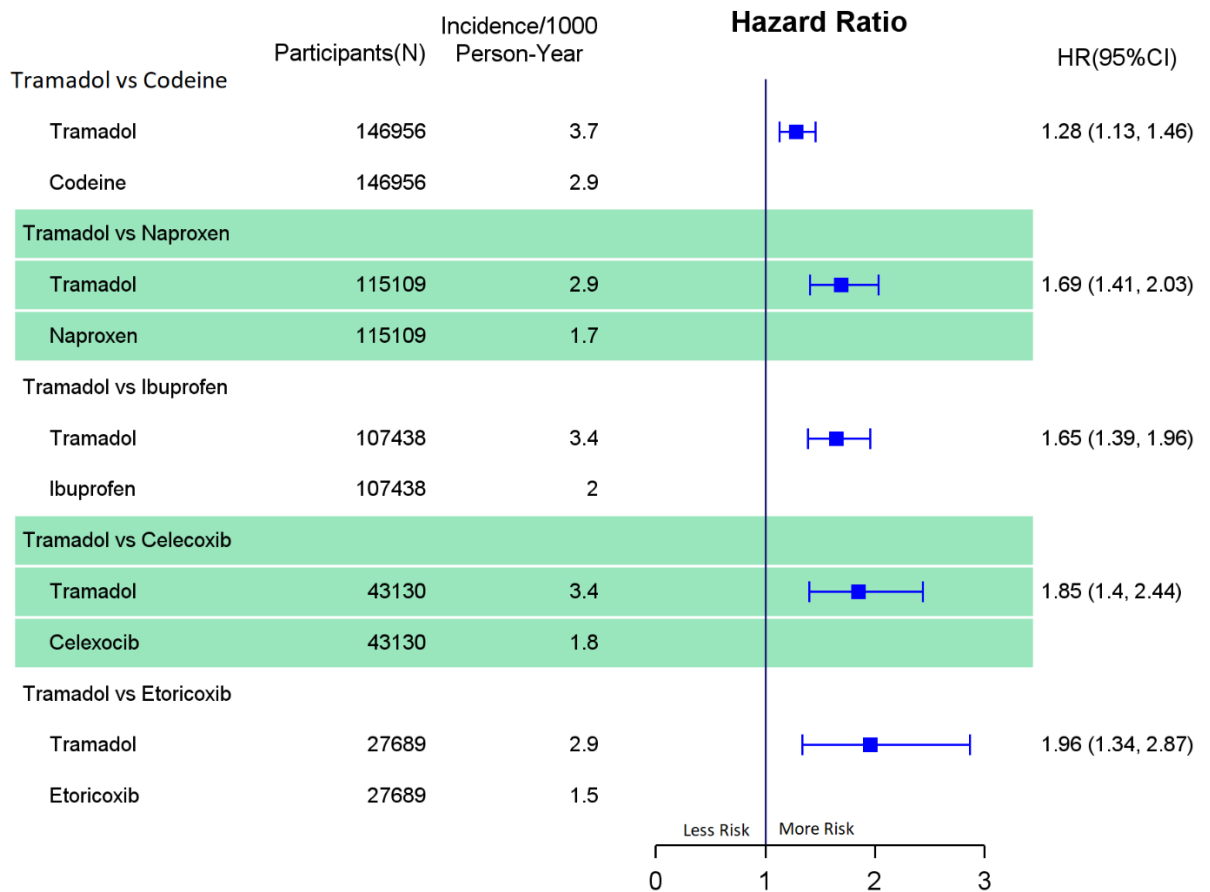
B. Underuse

1. Romanelli RJ, Ito MK, Karalis DG, et al. Statin utilization and low-density lipoprotein cholesterol in statin-treated patients with atherosclerotic cardiovascular disease: Trends from a community-based health care delivery system, 2002-2016. *J Clin Lipidol.* 2020;**14**: 305-314.

Optimizing Medication Use

1. Rieckert A, Reeves D, Altiner A, et al. Use of an electronic decision support tool to reduce polypharmacy in elderly people with chronic diseases: cluster randomised controlled trial. *BMJ*. 2020;**369**: m1822.
2. Romskaug R, Skovlund E, Straand J, et al. Effect of Clinical Geriatric Assessments and Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Home-Dwelling Older Patients Receiving Polypharmacy: A Cluster Randomized Clinical Trial. *JAMA Intern Med*. 2020;**180**: 181-189.
3. **Nace DA, Hanlon JT, Crnich CJ, et al. A Multifaceted Antimicrobial Stewardship Program for the Treatment of Uncomplicated Cystitis in Nursing Home Residents. *JAMA Intern Med*. 2020;**180**: 944-951.**
4. Sloane PD, Zimmerman S, Ward K, et al. A 2-Year Pragmatic Trial of Antibiotic Stewardship in 27 Community Nursing Homes. *J Am Geriatr Soc*. 2020;**68**: 46-54.
5. Sluggett JK, Chen EYH, Ilomäki J, et al. Reducing the Burden of Complex Medication Regimens: Simplification of Medications Prescribed to Long-term care Residents (SIMPLER) Cluster Randomized Controlled Trial. *J Am Med Dir Assoc*. 2020;**21**: 1114-1120.e1114.
6. Sluggett JK, Hopkins RE, Chen EY, et al. Impact of Medication Regimen Simplification on Medication Administration Times and Health Outcomes in Residential Aged Care: 12 Month Follow Up of the SIMPLER Randomized Controlled Trial. *J Clin Med*. 2020;**9**:1053.
7. O'Mahony D, Gudmundsson A, Soiza R. L, et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial. *Age Ageing*. 2020;**49**: 605-614.

8. Abbott RA, Moore DA, Rogers M, Bethel A, Stein K, Coon JT. Effectiveness of pharmacist home visits for individuals at risk of medication-related problems: a systematic review and meta-analysis of randomised controlled trials. *BMC Health Serv Res.* 2020;**20**: 39.
9. Almutairi H, Stafford A, Etherton-Beer C, Flicker L. Optimisation of medications used in residential aged care facilities: a systematic review and meta-analysis of randomised controlled trials. *BMC Geriatr.* 2020;**20**: 236.
10. Kirkham J, Maxwell C, Velkers C, Leung R, Moffat K, Seitz D. Optimizing Prescribing of Antipsychotics in Long-Term Care (OPAL): A Stepped-Wedge Trial. *J Am Med Dir Assoc.* 2020;**21**: 381-387.e383.
11. Martinez AI, Abner EL, Jicha GA, et al. One-Year Evaluation of a Targeted Medication Therapy Management Intervention for Older Adults. *J Manag Care Spec Pharm.* 2020;**26**: 520-528.



Supplemental Figure S1. Forest plot of hazard ratios for the association between tramadol use with risk of hip fracture. HRs and 95% CIs are from five separate cause-specific Cox proportional hazard models. HR, hazard ratio; CI, confidence interval. ¹⁷