**High-Risk Medication Use in Older Residents of Long-Term Care Facilities: Prevalence, Harms and Strategies to Mitigate Risks and Enhance Use**

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**Running title:** High-risk medication use in long-term care

**Keywords:** medication safety, adverse drug events, drug utilization, long-term care, residential aged care, nursing homes, homes for the aged, antipsychotic, opioid, insulin, glucose lowering medication, anticoagulant, antiplatelet

**Word count for abstract**: 102 words

**Word count for main text**: 4104 words

**Abstract**

Older residents of long-term care facilities (LTCFs), also known as nursing homes, care homes or residential aged care facilities, often have multiple health conditions and are exposed to polypharmacy. Use of high-risk medications such as opioids, glucose lowering medications, antithrombotics and antipsychotics is prevalent among residents of LTCFs. Ensuring appropriate use of high-risk medications is important to minimize the risk of medication-related harm in this vulnerable population. This paper provides an overview of the prevalence and factors associated with high-risk medication use among residents of LTCFs. Evidence-based strategies to optimize the use of high-risk medications and enhance resident outcomes are also discussed.

**Introduction**

Residents of long-term care facilities (LTCFs), also known as nursing homes, care homes or residential aged care facilities, account for 8% of the population aged ≥65 years in Australia.1 In the United States (US), an estimated 1.35 million individuals resided in a LTCF in 2016.2 This population, which is characterized by older age, multimorbidity, frailty, altered pharmacokinetics and pharmacodynamics, frequent care transitions, polypharmacy and high-risk medication use, is particularly vulnerable to medication-related harm.

High-risk medications, sometimes referred to as high-alert medications, are defined as medications “…associated with significant patient harm or death if they are misused or used in error”.3, 4 The APINCHS classification system (Box 1) is used to draw attention to high-risk medications in acute care settings in Australia, although other medications such as digoxin, antipsychotics, glucose lowering medications and neuromuscular blocking agents are also acknowledged to be higher risk in certain settings.5 At present, there is no standardized list of high-risk medications that applies to LTCFs. Box 2 outlines the medications considered by the Institute for Safe Medication Practices to be high-risk in LTCFs.6 Similarly, in community care settings, a recent systematic review reported that opioids, warfarin, heparin, hypnotics and sedatives, chemotherapeutic agents (excluding hormonal agents), methotrexate and glucose lowering medications were most frequently categorized as high-risk medications.7

Of these medications, opioids, glucose lowering medications, antithrombotics and antipsychotics are among the greatest contributors to medication-related harm among older people. Anticoagulants, glucose lowering medications and opioids were implicated in six of every 10 emergency department (ED) visits for adverse drug events (ADEs) in older people in the US.8 In another study in North Carolina LTCFs, opioids, glucose lowering medications and anticoagulants comprised three of the four medications classes that were most commonly implicated in medication errors in 2010-11,9 with warfarin, insulin and oxycodone implicated in the most serious errors.10

ADEs associated with high-risk medications are often preventable.11 In some cases, concern about potential ADEs with high-risk medications such as oral anticoagulants (OACs) may also contribute to under-prescribing among residents who could potentially benefit from treatment. Reducing harm arising with high-risk medications has been identified as an international health priority area. The *US National Action Plan for Adverse Drug Event Prevention* was developed to improve medication safety and patient outcomes by reducing harms associated anticoagulants (i.e. bleeding), glucose lowering medications (i.e. hypoglycemia) and opioids (i.e. accidental overdose, over-sedation, respiratory depression).11 Reducing harm arising from the use of opioids, insulin, anticoagulants and antipsychotics is one of the three flagship priorities outlined in Australia’s national response to *Medication without Harm*, the third World Health Organization Global Patient Safety Challenge.3

Pharmacists can make an important contribution to ensuring appropriate use of high-risk medications in LTCFs and mitigating the harms associated with the use of these medications. In this paper, we describe the prevalence and factors associated with the use of opioids, glucose lowering medications, antithrombotics and antipsychotics in LTCFs in Australia, the US and the UK, and potential harms associated with the use of these high-risk medications. We also summarize strategies that pharmacists and other health professionals can implement to minimize risks and enhance the use of these medications in LTCFs.

**Opioids**

Pain is a commonly reported symptom among residents of LTCFs. The prevalence of pain across LTCFs in the US, United Kingdom (UK), Canada and Australia ranges from 19% to 71%, and varies depending on the measured severity and persistence of pain.12-14 While paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are considered first line therapies for pain management, if pain persists, opioids may be considered for certain types of pain such as cancer pain and in selected residents with severe non-cancer pain.15, 16

The prevalence of opioid use ranges from 22.4% to 51.7% in residents of LTCFs17-25 (Table 1) and has increased globally, especially over the past two decades.26 Variability in prescribing may be driven by several factors. Clinicians who are more cautious about prescribing NSAIDs may prescribe opioids instead. Opioids may be prescribed for their sedative effects, not just for analgesia, or prescribed as an alternative to psychotropics in the management of the behavioral and psychological symptoms of dementia (BPSD).26, 27 Cultural factors and variability in pain assessment may also influence prescribing of opioids across facilities.26

Opioids are more likely to be prescribed to residents who are female,20, 23, 25 younger,17, 20 and have greater cognitive function.18, 23, 25 Certain types and severity of pain, disease states, depressive symptoms and level of physical function are also more likely to lead to opioid use, with severe and musculoskeletal pain, arthritis, osteoporosis, and greater physical impairment particularly indicated.20, 23, 25 Indeed, opioids are prescribed more often to people reporting current pain than those not.12, 19, 28

Concerns have also been raised relating to undertreatment of pain in some residents. This may relate to hesitancy among healthcare professionals to prescribe opioids to older residents (e.g. ≥85 years of age) and those with cognitive impairment due to concerns about ADEs and uncertainty of pain assessment, despite a similar prevalence of painful conditions in these individuals.13, 29

A range of opioids are prescribed to residents of LTCFs. Oxycodone is one of the most common opioids regularly prescribed in LTCFs (7.8-36.2%)17, 20, 21, 23, 25 along with buprenorphine (12.3-31.6%)21, 23, 25 and fentanyl (6.0-12.5%).17, 20, 23 Long-acting and transdermal opioid formulations are more likely to be prescribed in LTCF residents than community-dwelling older adults.30 The increased use of buprenorphine and fentanyl patches, while easy to administer, is of concern as potent opioids should be avoided in opioid-naïve residents, especially those who are cognitively impaired, due to risk of ADEs.31, 32 Consideration of renal function is also advised when selecting therapy as opioids such as morphine and tramadol can lead to the accumulation of active metabolites among older residents with impaired renal function. Use of an opioid conversion calculator is advised when changing the administration route or type of opioid.16

Opioids have been associated with a range of ADEs in LTCF residents, including constipation, nausea, dizziness and somnolence.33 A recent systematic review and meta-analysis reported opioids are associated with an increased risk of falls, fall-related injuries and fractures in older adults.34 This is particularly an issue with higher doses, more potent opioids, more frail residents and those with a prior history of falls.35-37 Opioids thus increase the risk of hospitalization in LTCF residents.38 Opioids are associated with cognitive impairment at higher doses and increased mortality in older adults.39 However, this has not been specifically established in the LTCF setting where people with serious cognitive impairment, speech and language problems and severe physical illness are often excluded from clinical research studies.40

Increases in opioid prescribing in LTCFs may reflect changes to prescribing guidelines and availability of products.25 However, this increase in prescribing does not necessarily equate to residents receiving the most appropriate therapy. Medication is often prescribed as needed, and administration depends upon staff and their ability to assess pain accurately.26 This is of particular concern for residents who are cognitively impaired and have difficulties communicating their pain. Further research is needed to optimize consistent pain assessment, the use of stepped pain management approaches, therapeutic and ADE monitoring, and deprescribing procedures. The use of non-pharmacological therapies, greater interdisciplinary collaboration, and optimizing opioid use in vulnerable subgroups, including people living with dementia, is needed.

**Glucose lowering medications**

An estimated 10-30% of residents of LTCFs are living with diabetes.41, 42 The majority of these individuals are living with type 2 diabetes, although the prevalence of type 1 diabetes in LTCFs is increasing.

There is a paucity of information about glucose lowering medication use, ADEs and health outcomes among residents with diabetes in LTCFs in Australia, the US and the UK. Between half and three quarters of all residents with type 2 diabetes are prescribed at least one glucose lowering medication (Table 1). Metformin and gliclazide are commonly prescribed oral therapies in LTCFs in Australia although up-to-date information from large scale studies are lacking. One US LTCF study conducted between 2008 and 2010 reported that sulfonylurea initiation was more common than metformin initiation.43 Shorter-acting sulfonylureas such as gliclazide and glipizide are preferred to long acting sulfonylureas (e.g. glimepiride) or those with renally excreted active metabolites (e.g. glyburide) when sulfonylurea treatment is deemed necessary.42, 44, 45 Many glucose lowering medications require dose reductions when used among residents with moderate to severe renal impairment to minimize the risk of hypoglycemia and other ADEs.42

The proportion of residents with diabetes that are treated with insulin, which is considered a high-risk medication across all health care settings, varies widely across LTCFs. A systematic review of 11 studies published between 2000 and 2012 reported the prevalence of insulin use in LTCFs ranged from 2.7% to 58.0%.46 The most common and concerning ADE associated with insulin is hypoglycemia, which can be more challenging to recognize in older residents and among people with cognitive impairment. Individuals aged ≥80 years who are treated with insulin have double the risk of an ED visit for insulin-related hypoglycemia and a five times greater risk of subsequent hospitalization compared to those aged 45-64 years.47 Problems with meal planning and insulin product mix-ups are the most common contributors to ED visits for insulin-related hypoglycemia in older people.47 The risk of insulin-related hypoglycemia may be further compounded in LTCFs, where most residents require assistance with medication administration and insulin may need to be administered to multiple residents at specific intervals before meals. Residents with coexisting diabetes and dementia may also have difficulty recognizing hypoglycemia symptoms and/or communicating symptoms to LTCF staff.44 The sole use of sliding scale insulin is not recommended in LTCFs due to the complexities associated with administration and monitoring, poorer glycemic control and risk of hypoglycemia.42, 45

Individualized treatment plans are crucial among residents with type 2 diabetes, who are at increased risk of ADEs with glucose lowering medications due to conditions such as reduced renal function, multimorbidity, frailty, dementia, weight loss42, 45 together with an increased rate of infections and care transitions. This individualized plan should include strategies to minimize the risk of hypoglycemia for that resident.48 Tight glycemic control may cause more harm than benefit in older residents with type 2 diabetes. Among older and more frail individuals, the focus of diabetes treatment typically shifts towards ensuring best-possible quality of life by minimizing adverse events and acute diabetes symptoms, rather than maintaining strict glycemic control.42 Many residents of LTCFs with type 2 diabetes and limited life expectancy and/or advanced dementia are potentially overtreated and may benefit from deprescribing of glucose lowering medications. A US study of 6960 veterans with diabetes and dementia or limited life expectancy who had a HbA1c measurement within 90 days of admission to a LTCF found 43.9% were potentially overtreated, with treatment deintensification observed among one third of these individuals in the following 90 days.49 Conversely, undertreatment with glucose lowering medications has also been observed in some residents of LTCFs, although this is less common.50 Further evidence to guide treatment decisions and deintensification of glucose lowering therapy in residents of LTCFs is needed, particularly among residents approaching the end-of-life, where existing guidance is largely based on expert opinion.

**Antithrombotics**

Antithrombotics (anticoagulants and antiplatelets) are high-risk medications owing to their potential to cause serious ADEs, namely hemorrhage. Antithrombotics are the most common cause of ADEs in community-dwelling older people, with bruising, bleeding or indigestion reported by 86% of individuals aged ≥70 years.51 The risks associated with antithrombotic use are intensified among residents of LTCFs. In accord, treatment decisions among residents of LTCFs are complex and must take into account polypharmacy, frailty, dementia, multi-morbidity, falls risk, altered pharmacokinetics and pharmacodynamics, and a simultaneously heightened clot and bleed risk profile.52

Antiplatelets are commonly prescribed in LTCFs for conditions such as coronary heart disease, myocardial infarction and ischemic stroke. In a retrospective study of 10,387 residents of UK LTCFs, 83.6% of those with coronary heart disease (n=1980) and 88.3% of residents with a previous ischemic stroke (n=1073) were prescribed aspirin (Table 1).53

Common indications for the use of OACs such as warfarin and direct oral anticoagulants (DOACs) (e.g. apixaban, dabigatran, edoxaban, rivaroxaban) in LTCFs include atrial fibrillation (AF), AF-related transient ischemic attack or ischemic stroke, or venous thromboembolism. AF is a condition that disproportionately affects older people, with a reported prevalence of 7.1% to 38% in LTCFs,54, 55 and is the primary indication for OAC use in this setting.56 The prevalence of OAC use in residents with AF ranged from 35.6% to 47.8% in three recent LTCF studies (Table 1).57-59 Among residents with previous ischemic stroke, a similar prevalence of OAC and antiplatelet use (33% and 34.8%) has been reported.60, 61

A systematic review of eight studies examining factors associated with antithrombotic use found that AF and previous stroke were independently associated with antithrombotic prescribing, while individuals with dementia were less likely to receive an antithrombotic.56 However, increased anticoagulant uptake has been observed among older people with Alzheimer’s disease following the introduction of DOACs.62 In other studies, previous stroke, transient ischemic attack or thromboembolism were the strongest predictors of OAC use in residents with AF.58, 59 Individuals with a HAS-BLED score of ≥3 (indicative of an increased likelihood for bleeding events) and non-white ethnicity were less likely to receive an OAC.58, 59 Examination of facility-level characteristics associated with antithrombotic use in US LTCFs showed anticoagulant prescribing was more likely in residents with AF in facilities located in Midwest US compared to the West58 and antithrombotic use was more likely in stroke survivors living in facilities that were part of a chain.61

Antithrombotic use in residents of LTCFs represents a treatment-risk paradox. Unlike many other high-risk medications, under-prescribing due to concerns about the perceived risk of hemorrhage among residents with frailty, cognitive impairment, multi-morbidity and prior falls has been reported.63 The consequences of under-prescribing can be catastrophic in older people with AF, which accounts for up to 25% of strokes and leads to more severe strokes and greater stroke-related disability.64, 65 One previous US study of 10 LTCFs, residents treated with warfarin only spent 50% of the time outside an International Normalized Ratio (INR) range of 2-3.66 This suggests strategies to improve the quality of INR control may be necessary among residents with AF who are prescribed warfarin as antithrombotic guidelines for AF management in the general population recommend to aim for a time in therapeutic range >70% when warfarin is utilized.67

Strategies to reduce the risks associated with OAC use include therapeutic monitoring (e.g. INR testing for individuals prescribed warfarin) and regular bleeding risk assessment. Residents of LTCFs are particularly vulnerable to prescribing errors with DOACs that can arise due to differences in approved treatment indications, bleeding risk and dosing in renal impairment.68 One study reported 44% of residents without renal impairment incorrectly received a low-dose DOAC and 44% with renal impairment received standard doses.57 Regular review of DOAC dose in line with renal function and weight is suggested for individuals prescribed these medications.69

Overall, antithrombotic use in residents of LTCFs is complex and subject to variability. Treatment decisions should be made on an individual basis after appropriate assessment of potential benefits and risks, and discussion with residents and family members. Further investigation of treatment outcomes and interventions to optimize prescribing in LTCFs is paramount.

**Antipsychotics**

Evidence from the US, the UK and Australia suggests the prevalence of antipsychotic use in LTCFs ranged from 19 to 22% (Table 1).70-72 Antipsychotics may be used for residents with severe mental health conditions such as schizophrenia or bipolar disorder, and are also used for BPSD. Although agitation and aggression are referred to clinically as BPSD, underlying pathology related to dementia may not be the cause. Behaviors referred under the umbrella term of BPSD are likely to be multifactorial and may be due to unmet needs.73 Furthermore, although positive experiences can arise from moving to a LTCF, for some residents this can be a distressing time and may result in changed behaviours.74

There are differences between countries regarding whether the use of antipsychotics for BPSD is off-label use and regulations for the duration of treatment. In the US, all use of antipsychotics for managing BPSD is off-label and a black box warning in the prescribing information denotes the increased risk of mortality associated with antipsychotic use in older people with dementia. In Australia, risperidone is indicated for up to 12 weeks for BPSD among people with Alzheimer’s disease and recent changes to subsidy regulations require prescribers to request authority approval to extend treatment beyond this time. Similarly, in the UK risperidone is licensed for the short-term treatment (up to 6 weeks) for BPSD in people with Alzheimer’s disease if the person poses a risk or the person has not responded to non-pharmacological approaches. However, extended durations of antipsychotic use have been observed in LTCF studies.75

The prevalence of severe mental health conditions for older people in LTCFs is low, with average estimates between 1-3% in US nursing homes.76, 77 The prevalence of dementia has been estimated between 50% and 75% in the US, UK and Australia, but the prevalence varies between individual facilities. Despite lack of approval and guideline recommendations for non-pharmacological approaches, concerns have been raised internationally that antipsychotics are in some cases used for older residents in LTCFs inappropriately to manage non-severe behaviors which may include walking with purpose, insomnia or uncooperativeness.78

Randomized controlled trials and observational studies have shown both typical and atypical antipsychotics are associated with an increased risk of death among people living with dementia.79, 80 Antipsychotics have also been associated with a higher risk of other adverse outcomes including falls and hospitalizations among people with dementia.81 Most previous studies examining these associations have been conducted with community-dwelling populations. Fewer studies have focused on people living in LTCFs, but some report similar findings to studies conducted within community-dwelling populations.82, 83

Variation in prescribing of antipsychotics in LTCFs has been observed in the US. Resident characteristics, facility characteristics and prescribing culture have been shown to account for some of this variation.84

International guidelines recommend non-pharmacological approaches should be used first-line for BPSD and evidence suggests non-pharmacological strategies may have similar small-medium effect sizes for BPSD compared to antipsychotic use, without the ADEs.85 Available non-pharmacological approaches include functional analysis-based interventions which are individualized interventions aimed at identifying unmet needs, causes and consequences of behaviour.86 However, there is a need for further research to determine the efficacy of functional analysis-based interventions for BPSD.86 Non-pharmacological approaches for BPSD should be person-centered and considered with the resident and their family members where appropriate. Where non-pharmacological approaches have failed, other pharmacological approaches might be appropriate before the consideration of antipsychotics. Citalopram and analgesia have been prioritized ahead of antipsychotics if pharmacological approaches are needed for people with BPSD.87 Similarly to the use of non-pharmacological approaches, the use of medications for people with BPSD should be person-centered and measures should be taken to identify underlying causes of the behaviors. If a trial of pharmacotherapy is deemed necessary, a comprehensive discussion with the person with dementia and/or their family members about the potential risks and benefits of treatment is recommended.88 Low starting doses are advised, along with regular monitoring of the symptoms of the condition and possible ADEs, and regular review of the need for pharmacotherapy.88, 89

**Strategies to optimize high-risk medication use and resident outcomes**

A range of strategies could be utilized to enhance the use of high-risk medications in the LTCF setting (Table 2, Box 3). Pharmacists often have a key role in these activities, which can include provision of interventions at the individual resident level, clinical governance or educational activities delivered at the facility or organizational level, and interventions delivered at the wider LTCF population level.

*Existing tools that can be applied at the individual resident level*

At the individual resident level, comprehensive medication reviews provide pharmacists the opportunity to assess the potential benefits and risks of high-risk medication use, and work collaboratively to resolve and prevent future medication-related problems for that individual.90 High-risk medications such as warfarin, glucose lowering medications and opioids contribute to complex medication regimens in LTCFs.91 Residents may benefit from a structured process of medication simplification using a validated tool such as Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE)92 that was recently tested in the SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) cluster randomized controlled trial.93

Tools for identifying potentially inappropriate prescribing in older people may be applicable to residents of LTCFs, including the American Geriatrics Society Beers, STOPP and STOPPFrail explicit criteria.94, 95 These tools can inform comprehensive medication reviews, but their clinical relevance should be assessed, evaluated and prioritized in the context of an individual’s clinical status and preferences.96

Risk assessment tools for specific conditions or medications can be applied at the individual level. The Australian *McKellar guidelines for managing older people with diabetes in residential and other care settings* contain assessment tools for diabetes-related risks such as hypoglycemia, falls, pain and glucose lowering medication-related ADEs.48 The Comparing Treatment Options for Pain (C-TOP) tool can be used during shared-decision making discussions with residents and family members to visually illustrate and discuss the potential benefits and possible harms associated with different treatments for pain, including opioids.97 Online calculators are available to assist with the calculation of total oral morphine equivalent doses to support decisions for rationalizing opioid use.98, 99 Numerous tools are available to estimate an individual’s risk of stroke (e.g. CHA2DS2-VASc) and major bleeding (e.g. HAS-BLED) to inform OAC treatment decisions for residents with AF.100, 101

Once the benefits and risks associated with individual medications and the cumulative risk from multiple medications have been identified for an individual resident, opportunities to address under-prescribing, or conversely, to reduce the dose or deprescribe high-risk medications can be discussed. Deprescribing is defined as the systematic process of identifying and discontinuing medications in instances where the existing or potential harms outweigh existing or potential benefits within the context of an individual’s care goals, functional capacity, life expectancy, values, and preferences.102 Deprescribing guidelines and algorithms have been developed to guide the safe and appropriate discontinuation of high-risk medications such as antipsychotics and opioids and this remains an important area for further research. For example, guidance has been developed by the Bruyère Research Institute Deprescribing Guidelines Research Team103 and the NSW Therapeutic Advisory Group.104 Additionally, NPS MedicineWise, an independent Australian organization that helps people make evidence-based decisions about medications, has developed a tool to facilitate multidisciplinary review of antipsychotics prescribed for residents experiencing BPSD, including advice on how and when to taper the antipsychotic.105 The NPS MedicineWise opioid tapering algorithm can assist with preparing a tapering plan for residents with non-cancer pain.106

*Population-based approaches targeting high-risk medication use in LTCFs*

There is a clear need to examine medication-related quality of care systematically and routinely in LTCFs given the high burden of medication use in this setting. Quality and safety monitoring systems that include medication-related indicators have been developed, validated and implemented internationally to measure, monitor, and ultimately improve quality of care in LTCFs.107, 108 Countries such as the US, Canada, Sweden and the Netherlands have implemented complex, mandatory, and in some instances public, LTCF reporting systems since the 1990s.107, 109-113 Ongoing monitoring by these systems can identify unwarranted variation in high-risk medication use, provide opportunities for benchmarking, and underpin quality improvement initiatives in LTCFs. When developing or choosing medication-related quality or safety indicators for use in LTCFs, it is important to consider the most important medication-related issues in those facilities (e.g. high-risk medications, medication use in limited life-expectancy), those that are likely to have the greatest impact on resident health outcomes, medication-related issues that potentially can be changed by stakeholders, and those that are meaningful to residents and family members (person-centered).114, 115 In accord, the most common medications assessed via quality and safety indicator monitoring systems include the use of antipsychotics without an appropriate indication, and sedative and hypnotic medications. Pharmacists and other health professionals can use indicator findings to inform targeted strategies to enhance the use of high-risk medications in LTCFs and track changes in medication use and/or appropriateness over time.

*Recent interventions to enhance use of high-risk medications in LTCFs*

Examples of specific interventions to enhance the use of opioids, glucose-lowering medications, antithrombotics or antipsychotics are described in Table 2. There is a paucity of interventional research specific to the optimization of opioid, glucose-lowering and antithrombotic medication use in LTCFs. Existing antithrombotic interventions have predominantly focused on improving warfarin management despite a shift towards increased DOAC use in LTCFs in more recent years. Conversely, there has been considerable and increasing focus on reducing antipsychotic utilization in LTCFs.

Common features of successful interventions described in Table 2 include close consultation and delivery as part of an interdisciplinary team that includes nursing, medical, pharmacy and LTCF staff. Most strategies targeted inappropriate medication use and showed significant reductions in the prescribing of high-risk medications post intervention. However, few studies assessed the clinical outcomes of these interventions. Those studies that did, however, mostly did not find meaningful impact on clinical symptoms or ADEs, including pain, falls and hospitalizations. Other outcomes that matter to residents and family members, such as resident quality of life, were infrequently assessed. This highlights the challenges in developing and implementing strategies that create clinically significant and sustained improvements in resident outcomes.

**Conclusion**

Use of high-risk medications such as opioids, glucose lowering medications, antithrombotics and antipsychotics is prevalent among residents of LTCFs. These medications can relieve symptoms or improve health outcomes if used appropriately in a patient-centered manner but are also associated with an increased risk of harm in this setting. Additional research on the benefits and risks of high-risk medications specific to the LTCF setting is needed, particularly for glucose lowering medications and antithrombotics. Existing evidence suggests it is possible to optimize the use of high-risk medications in LCTFs, although future work is needed to develop and test new interdisciplinary strategies suitable for delivery at the individual, facility and population level.

**Funding sources**

JKS is supported by an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship. ECKT is supported by a NHMRC-ARC Dementia Research Development Fellowship.

**Competing interests**

JKS and DR are pharmacists that are accredited to perform comprehensive medication reviews. DR is a Non-Executive Director of NPS MedicineWise.

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**Table 1. Prevalence of use of high-risk medications in long-term care facilities: characteristics of selected studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year** | **Study Design** | **Country and setting** | **Population** | **Study period** | **Method to assess medication use** | **Prevalence of use** | |
| **Opioids** | | | | | | |  |
| Hunnicutt et al., 201820 | Cross-sectional study | US LTCFs | 315,949 long-stay residents who were Medicare beneficiaries | Residents with an MDS assessment in April-June 2012 were followed for 120 days | Medicare Part D claims data | 32.4% overall (10.4% short-term use (i.e. 1-30 days), 6.5% medium-term (i.e. 31-89 days), 15.5% long-term (i.e. ≥90 days) | |
| Shah et al., 201222 | Cross-sectional | England and Wales, 326 GP practices | 10,387 residents that were registered for ≥90 days with their GP (mean age 85.5 years) | Residents registered between March 2008 and February 2009 | The Health Improvement Network (THIN) primary care database was used to examine prescriptions issued in the previous 90 days. | Age and sex standardized percentage: 22.4% (n=2,325 residents) in the last 90 days | |
| Tan et al., 201623 | Cross-sectional study | Australia, 6 LTCFs maintained by one provider | 383 residents; mean age 87.5 years and 44% with diagnosed dementia | Residents recruited in April-August 2014 | Details of all opioids administered in the previous 24 hours were extracted from medication charts | 28.7% | |
| Taxis et al., 201724 | Cross-sectional study | Australia, 26 LTCFs | 1,560 residents | Data collected in 2009 | Pharmacy supply data | 42.5% | |
| Kalisch Ellet et al., 201921 | Longitudinal study | Australia, all veterans in LTCFs | 14,237 veterans residing in LTCFs who were alive between 1 July 2015 and 30 June 2016 (median age 91 years) | 1 July 2015 to 30 June 2016 | Department of Veterans' Affairs administrative health claims data | 49.5% received at least one opioid over the 12 month-period, with a median of 225 (IQR 45-365) treatment days covered. | |
| **Glucose lowering medications** | | | | | | | |
| Haines et al., 2016116 | Cross-sectional study | Australia, 10 LTCFs in north-eastern Victoria | 108 residents with diabetes (out of 593 residents) | Single time-point in 2013 | Chart audit | 55.6% (n=60) residents received ≥1 glucose lowering medication (21.3% insulin, 34.3% oral therapy) | |
| Andreassen et al., 2016117 | Secondary analysis of baseline data collected for the CAREMED cluster RCT | UK, 30 LTCFs | 106 residents with type 2 diabetes (out of 826 residents) | Baseline data for participants collected between 2011 and 2013 | Extracted from LTCF records | 66.0% (n=70) residents received ≥1 glucose lowering medication (14.2% insulin only, 5.7% insulin + oral, 80% orals only) | |
| Patell et al., 2017118 | Cross-sectional study | US, 2 skilled nursing facilities | 200 residents with diabetes | Data collected for consecutive new residents in 2014 | Chart audit | 100% of residents received ≥1 glucose lowering medication (71% insulin only, 15.5% oral and insulin, 13.5% oral only) | |
| Lederle et al., 202050 | Retrospective cohort study | US Veterans Affairs LTCFs | 5,471 residents aged >65 years with type 2 diabetes and a HbA1c measurement | 2013 to 2015 | Veterans Affairs data | 73% were treated with ≥1 glucose lowering medication (approx. 9% metformin alone, 12% other orals without insulin, 16% short-acting insulin without long-acting insulin, 63% long-acting insulin ± short-acting insulin or orals) | |
| **Antithrombotics** | | | | | | |  |
| Alcusky et al, 2019 119 | Repeated cross-sectional study | US, LTCFs | December 2011: 33,959 (85 years [IQR 79-90]), December 2016: 37,787 (84 years [IQR 78-90]) Medicare beneficiaries with AF in LTCFs with ≥6 months Medicare enrolment | 1 July 2011 and 2016, 31 December 2011 and 2016 | Linked Medicare administrative files and MDS assessments | 42.3% received OAC in December 2011  47.8% received OAC in December 2016 | |
| Gill et al, 2019 58 | Cohort study | US, Centers for Medicare & Medicaid Services certified LTCFs | 21,877 Medicare beneficiaries (5% random sample) with AF in LTCFs for ≥101 days in 2007-2013 | 2007-2013 | Linked Medicare administrative files and MDS assessments | Across all study years, 36.2% (95% CI 35.6-36.8%) received an OAC | |
| Frain et al, 2018 59 | Cross-sectional study | Australia, LTCFs | 1,952 residents with AF (86.5 years [SD 6.9]) who received a comprehensive medication review between January 2008 and June 2012 | January 2008-June 2012 | Clinical  decision-making software (Medscope®). | Among the 927 eligible residents (CHADS2 ≥ 2 and no contraindications), 35.6% received OAC, 41.3% received antiplatelet only | |
| Shah et al, 2011 53 | Retrospective cohort study | UK, LTCFs | 10,387 residents in LTCFs registered for ≥90 days with their GP (including 1,980 with CHD, 1,073 with ischemic stroke) | 2008-2009 | THIN, primary care database | 83.6%c (95% CI 81.5-85.8%) received antiplatelet for CHD, 88.3%C (95% CI 85.6- 91.0%) received antiplatelet post-ischemic stroke | |
| Hughes et al, 2004 61 | Cohort study | US, LTCFs in 6 states | 15,791 residents with previous stroke admitted to LTCFs with ≥3 Minimum Dataset assessments | 1992-1996 | MDS assessment | 34.8% received antithrombotics (n=4353 prescribed on admission and continued thereafter, n=1144 prescribed after LTCF admission) | |
| **Antipsychotics** | | | | | | |  |
| Harrison et al., 202082 | Retrospective cohort study | Australia, all LTCFs with people receiving government subsidized care | 322,120 concession card‐holding residents who lived in a LTCF for ≥3 months. | 1 April 2008 to 30 June 2015 | Antipsychotics dispensed via the Pharmaceutical Benefits Scheme (PBS) and the Repatriation PBS in the year before and the year after LTCF entry were identified using relevant WHO ATC codes. | In first three months after entering residential aged care: 21.3% (95% CI 21.1–21.4%) | |
| Briesacher et al., 201371 | Retrospective cohort study | US, LTCFs | 1,402,039 residents | September 2009-August 2010. | Prescription dispensing data from a large, long-term care pharmacy (Omnicare Inc) that serves 48 states and half of all LTCF residents in the US. | 22.0% (95% CI 21.9%–22.1%) (n= 308,449) received 1 or more antipsychotics. | |
| Szczepura et al., 201672 | Retrospective study | UK, 616 LTCFs | 31,619 residents | 31 December 2012 | Point prevalence: the percentage of residents prescribed ≥1 antipsychotic at each time point. | Mean 19.0% (±15.2). | |

Abbreviations: ATC, Anatomical Therapeutic Chemical (ATC) classification; CHD, coronary heart disease; GP, general medical practitioner; LTCFs, long-term care facilities; MDS, Minimum Data Set; OAC, oral anticoagulant; RCT, randomized controlled trial; THIN, The Health Improvement Network; UK, United Kingdom; US, United States; WHO World Health Organization.

**Table 2. Selected interventions to enhance opioid, glucose lowering medication, antithrombotic and antipsychotic use in long-term care facilities**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author, Year** | **Study Design** | **Country** | **Intervention** | **Intervention dates** | **Target groups** | **Key findings** |
| **Opioids** | | | | | | |
| Redding et al., 2014120 | Prospective pre-post intervention | US | Pain symptom assessment and deprescribing using the Brief Pain Inventory Scale and Clinical Opioid Withdrawal Scale | 2 weeks post-onset of acute illness and 2-weeks post hospital admission and LTCF readmission | 66 people treated with opioids | 45 residents experienced 104 acute illnesses. Sixty-four opioid interruptions. No changes in pain scores or withdrawal symptoms after deprescribing compared to pre-intervention. Residents deprescribing had higher pain scores over time compared to non-deprescribing group. |
| **Glucose lowering medications** | | | | | | |
| Lega et al., 2020121 | Pre-post intervention | Canada | Educational intervention delivered to dieticians and nurses (n=2 workshops), care workers (2 workshops) and GPs (n=1 workshop) | Not stated | Nurses, dieticians, care workers and GPs from 2 LTCFs. The 2 LTCFs cared for 100 residents with diabetes. | Self-reported comfort with certain aspects of diabetes management and self-appraised knowledge increased post-intervention among nurses/dieticians and care workers. Small reductions in sliding scale insulin use were observed in both LTCFs in the 3 months post-intervention and the % of residents with diabetes with a HbA1c within 7.1-8.5% increased in 1 facility. |
| Yu and Batty, 2010122 | Pre-post mixed methods study | Canada | Diabetes education and self-efficacy training workshop with written cases; participants worked in groups of three and shared responses with wider group. | Not stated | GPs, pharmacists and nurses from 4 LTCFs (n=15) | Knowledge scores were increased at 3 months post-intervention (from 4.0 (95% CI 3.0-5.0) to 5.1 (95% CI 4.1-6.1) out of 8, p<0.05). No changes in participant intention or self-efficacy were observed at follow-up. Qualitative analysis showed the content was not sufficiently tailored to the participants stage of change. |
| Sjöblom et al., 2008123 | Prospective, non-randomized pre-post intervention with comparison group. | Sweden | Plasma glucose levels were monitored for 3 days, followed by withdrawal of oral glucose lowering medications. Insulin doses were halved if >20 units/day or withdrawn if <20 units/day. Plasma glucose and HbA1c were monitored post-intervention. | 2006 | All residents with type 2 diabetes with HbA1c ≤6% and taking glucose lowering medication from 17 LTCFs received a de-intensification intervention (n=32); all others with diabetes allocated to non-intervention group (n=66). | At baseline, mean HbA1c was 5.2% (SD 0.4) in the intervention group versus 7.1% (SD 1.6) in non-intervention group. At 6 months follow-up, mean HbA1c was 5.8% (SD 1.1) in the intervention group versus 6.6% (SD 1.4) in non-intervention group. Four residents left the study due to hyperglycemia. Mortality rates at 6-months: 16% intervention group, 21% non-intervention group. |
| **Antithrombotics** | | | | | | |
| Bereznicki et al, 2014 124 | Pre-post; proof-of-concept study | Australia | Point-of-care INR testing (CoaguChek XS) by LTCF staff. Results sent to GPs via the MedePOC computer program for dosing instructions. | Not stated | 24 residents on warfarin in 6 LTCFs | No significant improvement in TTR (from 58.9% to 60.6%, p= 0.79) or proportion of INR tests in range (from 57.1% to 64.1%, p= 0.21). |
| Field et al, 2011 125 | Cluster RCT | US | Warfarin management communication protocol using SBAR | 2007-2008 | 435 residents on warfarin in 26 LTCFs (n=13 intervention, n=13 usual care) | Intervention increased time in TTR by 4.5% (95% CI 0.3-8.7%) after adjustment, but did not improve obtaining follow-up INR within 3 days after INR value ≥4.5 (adjusted odds ratio [aOR] 1.02, 95% CI, 0.44-2.4) or prevent warfarin-related events (aIRR 0.87, 95% CI 0.54-1.4), serious preventable adverse warfarin-related events (aIRR 0.50, 95% CI 0.17-1.5), or potential adverse warfarin-related events (aIRR 0.77, 95% CI 0.45-1.3). |
| Papaioannou et al, 2010 126 | Pre-post feasibility study | Canada | Warfarin management using MEDeINR (web-based decision support tool) | Not stated | 128 residents on warfarin (without prosthetic heart valve) in 6 LTCFs | No significant improvement in TTR (from 65%-69%, p=0.14), percentage of time in supra-therapeutic (from 14%-11%, p=0.08) or sub-therapeutic range (from 21% to 20%, p=0.66). |
| Crotty et al, 2004 127 | Cluster RCT | Australia | Two pharmacist outreach visits focused on falls and stroke prevention | Not stated | 715 residents in 20 LTCFs (n=381 intervention, n= 334 usual care) | No significant difference in number of residents at risk of stroke on aspirin (adjusted relative risk 0.54, 95% CI 0.29-1.00) or number of residents with AF on warfarin (aRR 0.92, 95% CI 0.23-3.95). |
| **Antipsychotics** | | | | | | |
| Brodaty et al., 2018128 | Single-arm longitudinal study in a convenience sample of 23 LTCFs | Australia | Two components: (1) education/training of health care staff, and (2) individualized deprescribing protocol: 50% dose reduction every 2 weeks and ceasing after 2 weeks on the minimum dose, withdrawing one antipsychotic at a time, with risperidone (if prescribed) to be withdrawn last. | April 2014-October 2016 | GPs, pharmacists, and LTCF nurses for education/training. Residents with a terminal illness or very severe BPSD at baseline were excluded. Education of GPs, pharmacists, and RACF nurses. 139 residents were recruited. | The number of older residents taking regular antipsychotics over 12 months reduced by 81.7% (95% CI 72.4-89.0). Withdrawal was not accompanied by drug substitution or a significant increase in *pro re nata* antipsychotic or benzodiazepine administration. There was no change in BPSD or adverse outcomes (falls and hospitalizations). |
| Westbury et al., 2018129 | Prospective, longitudinal study in 150 LTCFs | Australia | Multi-strategic program comprising psychotropic medication audit and feedback, staff education, and interdisciplinary case review over 6 months. | April 2014 – March 2016 | Staff at each RACF were educated by the consultant pharmacist. Key prescribers were sent intervention information and guidelines and encouraged to discuss with the champion nurse. Academic detailing sessions were offered to GPs and nurse practitioners. Pamphlets on benzodiazepine and antipsychotic use, developed with consumers were disseminated by RACFs to residents/relatives. | Over the 6-month period, the proportion of residents prescribed antipsychotics declined by 13% (from 21.6% (95% CI, 20.4–22.9%) to 18.9% (95% CI, 17.7–20.1%)). There were also declines in the numbers of residents regularly prescribed benzodiazepines, the mean chlorpromazine equivalent dose, the mean diazepam equivalent dose. For 39% of residents prescribed antipsychotics and benzodiazepines at baseline, these agents had been ceased or their doses reduced by 6 months. There was no substitution by sedating antidepressants or pro-re-nata prescribing of other psychotropic agents. |
| Kalisch Ellet et al., 2019130 | Pre-post intervention analysis for veteran residents of LTCFs who were aged 65 years and over. | Australia | In 2015, approved product information for risperidone was amended to restrict use in people with Alzheimer’s disease and BPSD for a maximum twelve-week duration. | Pre intervention: 1 January 2012-31 July 2015. Post intervention: 1 August 2015-31 August 2017. | All prescribers in Australia. | The monthly trend of risperidone use pre intervention was −0.49% and post intervention was −1.74%. The relative effect was −26.07% (95% CI: −10.89% to −41.26%). |
| Carnahan et al., 2017131 | Quasi-experimental longitudinal study of 307 LTCFs that did not receive the Improving Antipsychotic Appropriateness in Dementia Patients educational program (IA-ADAPT) intervention and 112 facilities which did receive the intervention. | US | IA-ADAPT and Centers for Medicare and Medicaid Services Partnership to Improve Dementia Care (CMS Partnership) promote improved care for BPSD. | April 2012-December 2012. | Prescribers, nurses, direct care providers, and other providers. | Nursing home exposure to the IA-ADAPT was associated with reduced antipsychotic use (OR [95% CI] = 0.92 [0.89–0.95]). The CMS Partnership was associated with reduced antipsychotic use (OR [95% CI] = 0.96 [0.94–0.98]) No adverse impacts on BPSD. |
| Szczepura et al., 201672 | Retrospective analysis of 616 LTCFs | UK | National Dementia Strategy including recommendations such as older people could safely be withdrawn from agents like risperidone over 2–4-weeks with no adverse consequences and SGAs should be prescribed in preference to FGA agents; that the lowest possible effective dose should be prescribed for the shortest period (ideally <12 weeks); and that treatment should be reviewed at least monthly with reduction or cessation actively considered at each review. | 1 January 2009-31 December 2012. | All prescribers in UK. 31, 619 residents were included. | No statistically significant difference was observed in overall prescribing rates over the 4-year period (Kolmogorov-Smirnov (KS) test p=0.60), and there was no significant shift towards newer SGAs (KS test p=0.32). |
| Fossey et al., 2006132 | Cluster RCT of 12 specialist LTCFs | UK | Training and support intervention delivered to LTCF staff, focusing on alternatives to medications for the management of agitation in residents with dementia. | July 2003 to June 2004 | “Whole home” targeted. 338 residents included.  Training delivered over 10-month period. | At 12 months the proportion taking an antipsychotic in the intervention LTCFs was significantly lower than the control LTCFs (23.0% vs. 42.1%). The average reduction in antipsychotic use was 19.1% (95% CI 0.5% to 37.7%). No significant differences were found in the levels of agitated or disruptive behavioral symptoms between intervention and control LTCFs. |

Abbreviations: aIRR, adjusted incidence rate ratio; AF, atrial fibrillation; CI, confidence interval; FGA first generation antipsychotic; GP, general medical practitioner; INR, international normalized ratio; LTCFs, long-term care facilities; RACFs, residential aged-care facilities; RCT, randomized-controlled trial; RMMR, residential medication management review; SGA second generation antipsychotic; SBAR, Situation, Background, Assessment, and Recommendation; TTR, time in therapeutic range; UK, United Kingdom; US, United States.

**Box 1. The ANPINCHS high-risk medication classification5**

**A** Antimicrobials

**P** Potassium and other electrolytes

**I** Insulin

**N** Narcotics (opioids) and other sedatives

**C** Chemotherapeutic agents

**H** Heparin and other anticoagulants

**S** Systems (medication safety systems to improve safety)

**Box 2. Institute for Safe Medication Practices (ISMP) List of High-Alert Medications in Long-Term Care Settings6**

* Anticoagulants
* Chemotherapeutic agents (excl. hormonal agents)
* Oral hypoglycemics
* Insulins
* Parenteral nutritional preparations
* Opioids
* Digoxin
* Epinephrine (parenteral)
* Iron dextran (parenteral)
* Methotrexate (oral, non-oncology use)

**Box 3. Strategies that can be used to monitor and enhance the use of high-risk medications among residents of long-term care facilities**

* Medication reconciliation
* Comprehensive medication reviews
* Clinical pharmacy services
* Risk assessment tools
* Deprescribing guidelines
* Individualized deprescribing protocols
* Facility high-risk medication guidelines
* Medication advisory committees
* Standardized medication administration charts with specific sections for high-risk medications such as insulin or warfarin
* Alerts embedded within electronic medication management systems
* Medication incident monitoring systems
* Local champions
* Academic detailing
* Educational resources and staff training
* Audit and feedback activities
* Formal stewardship activities/programs
* Facility accreditation standards
* Quality indicators and benchmarking
* Multi-component quality improvement interventions
* Changes to approved product indications or labelling
* Changes to pharmaceutical subsidy criteria