

## Glucose Lowering Medicines and Older People with Diabetes: The Importance of Comprehensive Assessments and Pharmacovigilance

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### Abstract

Diabetes is a chronic incurable disease of high prevalence in older people due to changes in glucose homeostasis, diabetes-related complications and other comorbidities that affect physical and cognitive functioning and have implications for medicines use. Polypharmacy is common and represents a significant medicine and self-care burden, risk of medicine-related adverse events, and inappropriate prescribing. Some medicines used to treat diabetes such as insulin, sulphonylureas, warfarin and antiplatelet agents are known as 'high risk' medicines because of their association with adverse events.

Managing medicines is a complex process that requires particular knowledge and skills and strategies to proactively identify risks and plan care to reduce the risk such as following evidence based recommendations/guidelines, comprehensive assessment and monitoring, using decision support tools such as BEERs, STOPP and START criteria, and importantly, involving the individual and/or carers in medicine decisions to personalise medicines education and the medicine regimen.

### Key words:

Older people; Diabetes; Glucose lowering medicines; Pharmacovigilance; Quality use of medicines

### Introduction and Background to Diabetes

Diabetes is a chronic incurable disease of high prevalence in older people [1]. Most older people have type 2 diabetes (T2DM), some have long standing type 1 diabetes (T1DM) and some develop Latent Autoimmune Diabetes in Adults (LADA). T2DM is associated with loss of first phase insulin release and progressive loss of beta cell function; consequently insulin production gradually declines. Both changes contribute to hyperglycaemia. Insulin resistance and elevated postprandial blood glucose are features of overweight older people with T2DM [2]. Initially these people might benefit from Metformin and/or other glucose lowering medicines (GLM) but most eventually require insulin [3]. Lean older people usually require insulin soon after diagnosis, especially if they have significant weight loss and ketosis [2].

The changes in glucose homeostasis and in the counter-regulatory response to hypoglycaemia as well as other diabetes- and age-related changes such as declining renal and liver function and nutrition deficits influence medicine safety and medicine choices [3]. Long duration of diabetes is associated with complications that usually require medicines. However, increasing age and diabetes complications and their associated physical and cognitive functional changes complicates medicines management, especially medicines self-management and increase the self-care burden [3,4].

Despite their commonalities, older people with diabetes are highly individual: that is they are not a homogeneous group. Consequently, diabetes care, including the medicines regimen, must be designed in

collaboration with the individual (personalised) and when appropriate with their family carers [3,4,5]. The individual's health and functional status, social situation, health and general literacy, and available support from family and/or the community are important components of a comprehensive medicine assessment.

### Older People with Diabetes and Medicine-Related Vulnerability

*Prescribing in older people is a balance between managing conditions according to disease-based guidelines and addressing the patient's goals while at the same time avoiding medicine-related problems (Phillippa Binns).*

Medicine-related problems are common in older people and are associated with increased costs, hospital admissions and poor outcomes and recovery takes longer [6]. Over 60% of hospital admissions for medicine-related adverse events (AE) involve warfarin/antiplatelet agents, insulin and other GLM alone or in combination: many are preventable [6]. For example, Gurwitz et al. [7,8] suggested 27% of adverse medicine-related events in primary care and 42% in long term care could have been prevented. Most of the problems occur during prescribing and monitoring. Medicine errors and AEs are associated with falls, delirium, geriatric syndromes, confusion, incontinence and frailty and death [7,8,9]. Common errors include prescribing inappropriate medicines and/or inappropriate doses (under and overprescribing) and not reducing doses as renal and liver function declines. Both under and overprescribing can result in AEs [10].

Over prescribing GLMs or GLM doses can cause hypoglycaemia; under prescribing contributes to hyperglycaemia, although the

underlying causes of both states are multifactorial. Hyperglycaemia is often not regarded as a medicine side-effect or AE in older people, particularly in aged care homes (ACH) [9]. Hyperglycaemia has significant short term effects on memory and cognition and causes fluid and electrolyte changes that predispose T1DM to ketoacidosis and T2DM to hyperosmolar states (HHS); both these states have serious consequences including death. In the longer term, hyperglycaemia causes damage to tissues and organs and exacerbates existing diabetes complications, other comorbidities and the ageing process [11].

Older people living in ACH are among the most vulnerable members of the population. Forty percent of older people in ACHs and 20% living in the community are prescribed at least one inappropriate medicine [9]. The focus in ACHs is often on administering medicines, which is a challenging and time consuming task for staff, especially given the staffing and resource issues in many ACHs. Other key medicine-related activities are often suboptimal, for example not timing GLM doses to correspond with meals and not timing blood glucose tests to the GLM action profile.

## The Imperative for Pharmacovigilance

*It is impossible to separate the chance of good from the risk of ill (David Hume).*

Managing medicine is complex. Many health professionals often focus on prescribing and administering medicines and patient non-adherence to medicines. Inappropriate prescribing including prescribing potentially inappropriate medicines (PIMS) for older people is common [12-14]. PIMS are still prescribed as first line management for vulnerable people even when evidence suggests their use leads to poor outcomes [15,16]. Many PIMS are appropriately prescribed according to individual needs at the time. The issue is that they are often not stopped when the acute episode resolves. If PIMS were stopped when they are no longer required many unintended consequences could be avoided. Usually, the risks associated with PIMS outweigh the benefits, especially when safer options are available. In some cases a safer option could be a non-medicine option; for example, Cognitive Behavioural Therapy (CBT) or acupuncture to manage pain.

As mentioned, medicine-related AEs are common reasons for hospital admissions. Many PIMS and medicines that are actually inappropriate (AIM) are prescribed during the hospital stay, often in intensive care units (ICU) [12,13]. Older people who survive ICU frequently experience polypharmacy, have several transitions to other wards/units during an admission, and are at high risk of AEs after discharge [12]. Morandi et al. [12,13] found 85% of older ICU survivors were discharged from hospital on one or more PIMS and > 50% were discharged with one or more AIM.

It is important to acknowledge the medicines may have been appropriate choices in the acute phase of the illness and responses to medicines are closely monitored in ICU, but the medicines may not be appropriate when the illness resolves. This scenario highlights the essential need to constantly review the medicine regimen when health status fluctuates and for proactive medicine reconciliation. Commonly prescribed PIMS are opioids, anticholinergics and antidepressants, which cause confusion, cognitive impairment and falls. These doses and dose frequency of these medicines are likely to be inappropriate at discharge [12,13,15].

People over age 65 use more medicines than any other age group: 90% use at least one medicine and 50% use  $\geq 5$  medicines [17]. A point prevalence survey in our hospital in Geelong, Australia suggests older people with diabetes use an average of 7 medicines in multiple doses throughout the day: range 1-17 [18]. In addition, they frequently use 1-5 complementary medicines especially vitamin and mineral supplements [14,18]. Thus, polypharmacy represents a significant medicine self-care burden and is common for many older people with diabetes. It is also associated with increased health care costs [19].

Polypharmacy is defined in various ways, but the term usually refers to using > 5 medicines concurrently; however it is also defined as older people 'taking multiple unnecessary medicines' [20]. The term has negative connotations because of the associated risk of medicine errors and AEs. Diabetes-related polypharmacy usually evolves over time due to the progressive nature of T2DM and the development and progression of diabetes complications that require medicines. Evidence shows that polypharmacy represents a major AE risk after discharge from hospital [9]. Box 1 outlines common causes of polypharmacy.

### Box 1: Some key factors that contribute to polypharmacy

- Lack of knowledge on the part of the prescribers and the individual for whom the medicine/s was prescribed.
- Increasing age because the progressive nature of T2DM, diabetes complications and other comorbidities that affect physical, cognitive and sensory function and usually require medicines.
- Older people who self-diagnose and self-medicate using non-prescribed medicines, medicines prescribed for a previous illness or another person, and complementary medicines.
- Prescribing cascade where medicines are prescribed to manage symptoms rather than the underlying cause of the symptoms and/or not stopping unnecessary medicines.
- Inadequate communication among health professional carers and with the individual that contributes to the prescribing cascade, especially if medicine reconciliation is not undertaken.
- Inappropriate/inadequate assessment and clinical monitoring.
- Admission to hospital, especially ICU, and transfer among care settings.

Because of the multifactorial metabolic derangements that need to be managed, one could argue that polypharmacy could actually be best practice for some people with diabetes. However, as the number of medicines increases, the likelihood of PIMS and AIMs being prescribed also increases [19] and the risks outweigh the benefits because older people have increased susceptibility to medicine side effects and are more likely to develop medicine toxicity than younger people [19].

It is possible that the prescribing cascade that leads to PIM/AIM prescription occurs when prescribers do not consider whether a new medicine is needed, whether some existing medicines could be stopped, especially if they are PIMS/AIMs or whether a non-medicine option is a safer and equivalent choice. Several age- and diabetes-related changes affect medicine safety and the risk/benefit ratio and, therefore, need to be considered when making medicine choices [11], (Table 1)

Issue	Possible consequences
<p><b>Polypharmacy, which is common in older people with diabetes</b></p>	<p>Medicine-medicine interactions and food-medicine interactions.</p> <p>Risk of prescribing potentially inappropriate medicines (PIMS) and actually inappropriate medicines (AIMs) especially when multiple prescribers are involved.</p> <p>Risk of presentation to emergency department/admission to hospital.</p> <p>Medicine self-management burden and non-adherence that may make medicines more or less effective but could reduce some potential adverse effects</p>
<p><b>Age- and diabetes-related effects on the gastrointestinal system</b></p> <p><b>Autonomic gastric neuropathy</b></p> <p><b>Under and over nutrition</b></p> <p><b>Changed appetite, dysphagia</b></p> <p><b>Malabsorption—food and medicines</b></p> <p><b>Reduced gastric acid production</b></p> <p><b>Reduced saliva production</b></p> <p><b>Nausea and vomiting</b></p>	<p>Reduced appetite due to age and some medicines increase the risk of hypoglycaemia and further reduce the already compromised ability to mount a counter-regulatory response to hypoglycaemia.</p> <p>People over 70 years often have nutritional deficits such as low protein stores (muscle mass), and vitamin D, B 12, C, E and calcium, and magnesium deficits</p> <p>Weight loss may not be appropriate in overweight older people because of the associated loss of muscle mass and strength and the risk of sarcopenia and associated falls risk, .</p> <p>Some oral glucose lowering medicines stimulate appetite, which may be positive for some older people.</p> <p>Nausea, vomiting and bloating may impair medicine absorption from the gut; alternatively it can be a side effect of many medicines and/or illnesses.</p> <p>Using medicines that delay or increase absorption of medicines or nutrients from the gut when the individual has existing gastrointestinal comorbidities for example: antacids and Metformin, which reduces vitamin B12 absorption in some individuals; antibiotics and Phenytoin reduce folic acid absorption; corticosteroids, thiazide diuretics and some antipsychotic medicines contribute to hyperglycaemia.</p> <p>Hyperglycaemia, protein deficits and weight loss lead to low serum protein and body water, which affects medicine binding, consequently more free medicines are in the circulation.</p> <p>Weight gain and increased deposition of body fat leads to increased storage of fat-soluble medicines and delayed elimination resulting in unpredictable action profiles.</p> <p>Difficulty swallowing some medicines, which can lead to non-adherence or inappropriate medicine crushing.</p> <p>Difficulty distinguishing hyperglycaemia-related dry mouth from medicine side effects.</p> <p>Increase risk of some medicines damaging tooth enamel.</p> <p>High fibre diet can increase gut transit time and reduce medicine absorption.</p> <p>Enteral and supplementary feeds may be needed if the individual has swallowing difficulties or is frail.</p> <p>The medicine dose form may need to be changed e.g. large sized tablets that are difficult to swallow and medicines that should not be crushed because they irritate the gut and their action profile will be changed.</p>
<p><b>Reduced renal function</b></p> <p><b>Increased renal threshold for glucose</b></p>	<p>Compromised renal function leads to reduced medicine clearance and more circulating medicine in the blood.</p> <p>Renal anaemia.</p> <p>Risk of kidney damage with some medicines including complementary medicines and investigative procedures involving radio contrast media.</p> <p>Microalbuminuria is associated with dementia, which inhibits medicine self-care and decision-making and increases hypoglycaemia risk.</p> <p>Macroalbuminurea predicts hypoglycaemia.</p> <p>HbA1c is less reliable in the presence of renal disease and anaemia.</p> <p>Dialysis might be needed in end stage renal disease.</p> <p>Glucose urine tests are unreliable.</p> <p>Urine glucose testing is not appropriate to detect hypoglycaemia</p>
<p><b>Liver damage is common in older people</b></p>	<p>Reduced metabolism of some medicines.</p> <p>Monitor liver function.</p>
<p><b>Reduced cardiac output and reduced peripheral blood flow</b></p>	<p>Delayed medicine transport to target tissues, therefore delayed action and effectiveness</p>

<b>Silent MI and sudden death</b>	<p>Increased medicine in the circulation and longer duration of action.</p> <p>Fluid retention, which affects medicine uptake in the tissues.</p> <p>Hypoglycaemia precipitates cardiac events such as MI and arrhythmias, which are secondary to autonomic activation of the counter-regulatory response to low blood glucose and results in haemodynamic changes, vasoconstriction, intravenous coagulability and viscosity.</p>
<b>Inadequate, inappropriate support from others</b>	<p>Isolation, people who have limited social contact and support are more likely to become depressed and non-adherent to the management plan, particularly medicines.</p> <p>Reduced intake.</p>

**Table 1:** Issues that can influence prescribing, administering and monitoring glucose lowering medicines in older people with diabetes and some possible consequences.

### Some Common Medicine-Related Issues in Older People

Many older research trials do not include older people or only include relatively healthy older people and those using none or one medicine, thus it is difficult to generalise the findings to frail older

people. [3]. Excluding older people from clinical trials is not a new phenomenon [21]. There is strong evidence that many medicines commonly prescribed for older people should be used with caution or not prescribed [9,15,16,22,23]. Table 2 outlines some medicines commonly used to manage diabetes in older people and their associated risks.

GLM class	Associated risk	Comments
<b>Metformin is often considered to be first line therapy for overweight people with T2DM.</b>	<p>Gastrointestinal disturbances are common.</p> <p>Anaemia due to reduced absorption of vitamin B12.</p> <p>Lactic acidosis is rare. It is a normal adaptive physiological response but if the compensatory response is overwhelmed lactate accumulates and acidosis can occur.</p>	<p>Start at a low dose and slowly titrate to reduce gastrointestinal effects.</p> <p>Reduce the dose if creatinine clearance 30–60 mL/min and use with caution or cease if it is &lt; 30 mL/min.</p>
<b>Sulphonylureas</b>	<p>Hypoglycaemia especially with long acting medicines e.g. Glibenclamide, which has been withdrawn from the market in some countries.</p> <p>Hypoglycaemia risk increases with increasing age due to changed counter regulatory response to low blood glucose and predominance of neuroglycopenic symptoms, which can be mistaken for confusion, delirium and other cognitive deficits.</p> <p>Some blunt myocardial preconditioning</p> <p>Increased appetite.</p>	<p>Hypoglycaemia contributes to falls risk, cognitive impairment in the short term (working and delayed memory) and dementia in the long term.</p> <p>Increased appetite might be appropriate in some older people.</p> <p>Long acting formulations such as Diamicon MR should not be crushed for administration.</p> <p>It is important to avoid hypo and hyperglycaemia, the blood glucose target range should be individualised But generally 6–15 is safe unless the person has hypoglycaemic unawareness.</p> <p>HbA1c targets should also be individualised considering functional status:</p> <p>Functionally independent: 7–7.5% (53–57 mmol/mol)</p> <p>Functionally dependent 7.5–8% (53–64 mmol/L)</p> <p>Frail and/or dementia up to 8.5% (up to 70 mmol/mol).</p>
<b>Meglitinides</b>	<p>Rapid insulin release and short duration of action.</p> <p>Low hypoglycaemic risk.</p>	<p>May be useful in older people but are not subsidised in some countries.</p>
<b>Thiazolidiones (TZD)</b>	<p>Peripheral oedema</p> <p>Myocardial infarction (Rosiglitazone increases LDL-c)</p> <p>Heart failure risk</p> <p>Congestive cardiac failure</p> <p>Weight gain</p> <p>Reduce white and red blood cell count</p> <p>Worsens macular degeneration</p> <p>Risk of bladder cancer with Pioglitazone</p>	<p>Contraindicated in New York Heart Foundation heart disease grades 3 and 4 and in the presence of oedema.</p> <p>Could reduce liver function. Test liver function before commencing and at regular intervals while on TZDs.</p>

	Fractures in the extremities especially in women	
<b>Glucagon-Like Peptide-1 (GLP-1)</b>	Flatulence and bloating and other gastrointestinal disturbances. Nausea. Long term risk of pancreatitis Induce weight loss in some people.	Not extensively studied in older people, consequently more research is needed in older people.  Might improve cardiovascular risk by reducing triglycerides and low density lipoprotein (LDL) Weight loss might not be desirable in frail older people. Low risk of hypoglycaemia unless combined with some Sulphonylureas or insulin. Injectable form may not be acceptable to some older people.
<b>Dipeptidyl peptidase 4 (DPP-4)</b>	Flatulence Gastrointestinal disturbances	Not extensively studied in older people, consequently more research is needed in older people.  Low risk of hypoglycaemia unless combined with some Sulphonylureas or insulin. But DPP-4 agents delay gastric emptying, which delays glucose entry into the blood stream, thus if hypoglycaemia does occur it can be prolonged.  Low risk of medicine interactions: Saxagliptin has the highest risk.
<b>Sodium/glucose cotransporter-2 (SLGT-2)</b>	Urinary tract and genital infections Polyuria in volume sensitive people Some agents are less effective in the presence of renal impairment	More research is needed in older people.
<b>Insulin</b> <b>Short</b> <b>Rapid</b> <b>Long acting analogues</b> <b>Premixed</b>	All are associated with hypoglycaemia risk. Some represent greater risk than others	Long acting analogues cannot be mixed with other insulin  They have a lower hypoglycaemia risk than many other insulins. Health professionals need to understand the action profile of each insulin class to prescribe safely and monitor appropriately.  Older people often require insulin because of progressive beta cell loss  Sliding insulin scales to manage hyperglycaemia is contraindicated  Can be administered using insulin pens, syringes, insulin pumps and continuous infusions in acute settings e.g. HHS

**Table 2:** Commonly used glucose lowering medicines (GLM), antihypertensive and lipid lowering medicine classes and their related risks. Some commonly prescribed GLMs are classified as high risk medicines e.g. insulin. Healthy diet and exercise are still necessary even when medicines are needed.

**Key issues include:**

*Hypoglycaemia* is a significant risk with insulin and some sulphonylureas, especially long acting preparations [2,15,16,24]. Older people with both T1DM and T2DM are particularly vulnerable to hypoglycaemia: it is the most frequent metabolic complication in older people and may account for one in five hospital admissions in older people with diabetes aged 80 years and older [25]. The GLM prescribed, often the long acting sulphonylurea glibenclamide, may have been inappropriate in a large number of people who had dementia and/or renal failure in Greco et al’s study [25].

Hypoglycaemia is associated with longer hospital stay and increased costs in T2DM [26]. It is often difficult to detect in older people because neuroglycopenic symptoms predominate and can be misinterpreted for confusion and not treated. Significantly, hypoglycaemia is associated with short term changes in delayed and working memory [27] and dementia in the longer term [28, 29] and can precipitate myocardial infarction [30], which might be ‘silent’

(present with atypical symptoms). The ability to mount a counter-regulatory response to hypoglycaemia declines over time and the glucagon response is virtually absent in many older people [26] and when the individual is malnourished and has limited glucose stores. Macroalbuminuria predicts severe hypoglycaemia [31]. Common causes of hypoglycaemia are shown in box 2.

**Box 2:** Hypoglycaemia risk factors in older people

- Age.
- Prescribed GLMs especially some sulphonylureas and/or insulin.
- Long duration of diabetes, which is associated with progressive changes in the counter-regulatory response to hypoglycaemia, in particular diminished secretion of glucagon and growth hormone, which contributes to hypoglycaemia unawareness.
- ‘Tight’ blood glucose control.
- Renal and liver disease.
- Nutritional deficits.

- Cognitive impairment and dementia, which make it difficult for the individual and health professionals to recognise hypoglycaemia.
- Multiple diabetes complications and other comorbidities that cause functional deficits and compromise diabetes-self care.
- Most current hypoglycaemia education programs and policies are not tailored for older people e.g. the focus on adrenergic hypoglycaemia symptoms such as sweating and trembling when neuroglycaemic symptoms such as confusion and behaviour change are more common in older people and contribute to hypoglycaemic unawareness.
- History of severe hypoglycaemia.

*If health professionals, the person with diabetes or family carers do not consider medicine side effects* as the cause of symptoms, medicines can be prescribed to treat the symptom (prescribing cascade) and increase the likelihood of adverse events. Determining the cause of symptoms can be difficult because they are often non-specific and atypical.

*Declining renal function* and chronic kidney disease is common in older people with diabetes and is a predictive risk factor for medicine AEs [24] especially hypoglycaemia and falls [11]

*Antipsychotic medicines* when they are prescribed to manage behavioural problems associated with dementia.

*Antihypertensive medicines* that carry risk of postural hypotension and can lead to falls.

*Some lipid lowering agents* are contraindicated if liver disease is present. Liver function declines with age. Therefore, monitoring liver function is an important aspect of medicine management.

*Sliding insulin scales* to manage hyperglycaemia [15, 16]. Sliding insulin scales might lower the blood glucose, but they do not address the preceding factors that led to hyperglycaemia such as infections (urinary tract, foot infections), diet, stress, pain, depression that need to be treated otherwise hyperglycaemia could lead to hyperosmolar states (HHS), confusion, delirium, falls, reduced quality of life and symptomatic discomfort [4,15]. That is, it is essential to treat the cause rather than just reacting to the symptom, hyperglycaemia. For these reasons the trend is not to use sliding insulin scales in routine care, although they may still be indicated in acute illnesses such as DKA and HHS in an insulin infusion.

*Blood glucose is often tested infrequently* in ACHs and/or the testing schedule is not related to key medicine safety factors such as meal times and glucose lowering medicine action profiles, especially peak action times for insulin.

Many medicines prescribed to manage diabetes and its complications are classed as high-risk medicines because of their side effects and the way they are used and metabolised in the body, for example insulin and anticoagulants [32]. High risk medicines have a significant risk of causing catastrophic harm when used in error. However, as the information presented so far shows, high risk medicines can also cause significant harm when used appropriately if their effects are not monitored closely and when the dose and/or dose regimen is not safe for the individual.

**Box3: Examples of some commonly prescribed medicines that can increase or lower blood glucose. Medicine availability changes as older medicines are discontinued or removed by regulatory authorities. The**

**information in this box was current at the time of publication. Detailed information can be obtained from:**

- <http://www.diabetesincontrol.com/tools/tools-for-your-practice/9625-drugs-that-can-affect-blood-glucose-levels>
- *Medicines that increase blood glucose* are known as diabetogenic medicines. Diabetogenic medicines also increase blood glucose in older people at risk of diabetes. Some of these medicines are PIMs/AIMs but they may be appropriate treatment for the individual's illness at the time. The individual and their carers should be informed about the potential effect on blood glucose when medicines that increase blood glucose are commenced and what to do if the blood glucose is affected. Blood glucose monitoring is useful to detect changes early. Medicines should be used at the lowest effective dose for the shortest possible time and in the least diabetogenic dose form. It is important to manage the hyperglycaemia to reduce the associated risks such as dehydration, delirium, falls, incontinence and candida infections e.g. corticosteroids. Examples include:
  - Corticosteroids especially long acting oral preparations.
  - Antipsychotics especially atypical antipsychotics.
  - Sympathomimetics such as adrenaline and salbutamol.
  - Thyroid and growth hormones.
  - Thiazide diuretics.
  - Some antihypertensive medicines such as atenolol, carvedilol and metoprolol.
  - Some herbal medicines such as Chrysanthemum extract, Honey bee pollen, Tamarind. Note: people generally use these medicines to treat intercurrent illnesses not to manage blood glucose. Significantly, most of the information is based-on single case reports, which do not provide the botanical names of the herbs in the medicine.
- *Medicines that lower blood glucose* in addition to GLMs Determine the individual's hypoglycaemia risk before commencing medicines that can increase the hypoglycaemia risk or mask hypoglycaemia symptoms. The individual and their carers should be informed about the potential effect on blood glucose when medicines that increase blood glucose are commenced and what to do if the blood glucose is affected. Blood glucose monitoring is useful to detect changes early. Examples include:
  - Sulphonamides
  - Salicylates
  - Warfarin
  - MAO inhibitors
  - Tuberculostatics.
  - Herbal medicines that can lower the blood glucose include Aloe, Ginseng, *Momordica charantia* (Bitter melon), *Trigonella foenum graecum* (Fenugreek) and *Opuntia* species (prickly pear) especially if they are combined with conventional GLMs. Note: there is some reasonable quality research to support the glucose lowering effects of these medicines.
  - Alcohol.
  - Note: some medicines can cause either hyp- or hyperglycaemia e.g. magnesium salicylate, Lithium, Lanreotide.

## Strategies that can to Improve Medicine Safety and Reduce Medicine-Related Adverse Events in Older People with Diabetes

*Who assess well, treats well* (Fundamenta Medica).

Regular comprehensive medicine assessments and medicine reconciliation are essential, especially when several doctors prescribe medicines for the same person [24]. A medicine assessment must include information about the individual's medical and medication history, health status, physical functioning as such as Activities of Daily Living (ADL) Instrumental Activities of Daily Living (IADL) Geriatric Discussion Scale, cognitive function such as Mini Mental State Examination (MMSE) and sensory status (vision and hearing), social circumstances and available support, especially if the individual lives in the community. Home medicines reviews can elicit important information about the social factors that affect medicine self-management.

Medicine assessments should aim to identify key related risks such as PIMs/AIMs, duplicate prescriptions, and CAM and over-the-counter (self-prescribed) medicine use, hypoglycaemia, hyperglycaemia, other adverse events, falls, pain, and self-care capacity. It is essential to maintain up-to-date medicine histories and medicine lists and communicate any changes to everybody involved in the individual's care, the individual and his or her family carers in a timely manner and using appropriate language and design/format for written material.

As indicated, it is important to monitor liver and renal function, which decline with increasing age: most people over age 60 have liver and renal function changes [33]. These changes affect medicine choices. It is important to stop or reduce the doses of medicines such as ACE, NSAIDs and Cox-2 inhibitors that contribute to declining renal function. Antituberculosis medicines and alcohol affect liver function. It is important to regularly monitor renal and liver function, especially when such medicines are needed.

The medicine regimen should be reviewed every time a medicine is started or stopped, an adverse event occurs or health status changes. An admission to hospital is an ideal time to undertake a medicines review and assess their understanding of their medicines and their medicine self-management capacity. Admission and discharge between wards/units and between care settings are high risk times: medicine reconciliation should occur at every transition [12,13].

The general practitioner and other carers can contribute important information to medicine reviews and should be informed about the outcome of any medicine review and changes to the medicine regimen. The medicines review must include complementary and alternative therapies (CAM) because people with diabetes are high CAM users [34]: some CAM are beneficial, safe non-medicine options.

Quality use of medicines (QUM) [35] is a useful framework for using the information from comprehensive assessments to make decisions about the medicine regimen, doses and dose frequency. Importantly, QUM encompasses the entire medicine pathway (from bench to bedside), regulatory processes, labeling, and advocates using non-medicine options when they are safe and evidence-based.

Several decision support tools are available to help health professionals manage medicines for/with older people. These include:

BEERS criteria [15]

Screening Tool to Alert doctors to the Right Treatment (START) [22]

Screening Tool of Potentially inappropriate Prescriptions (STOPP) [23]

Medication Appropriateness Index (MAI) [36]

Australian Inappropriate Medication Use and Prescribing Indicators Tool [36,37]

Guidelines such as National Institute of Clinical Excellence (NICE) [38], National Prescribing Service (NPS) [24] The McKellar Guidelines [4] and the International Federation Global Guideline for Managing Older People with Type 2 Diabetes [3].

Various medicine AE risk assessment tools such as Medicines Risk Screen (NPS) [39], the GLM-related Adverse Event Risk Assessment Tool [4].

High Risk Medicine Alerts [32].

However, it is essential to prescribe medicines appropriate for the individual's clinical context when using these decision aids and alerts. Making decisions in collaboration with the multidisciplinary team facilitates appropriate in individualised prescribing [3,4,12,13]. Where possible the individual is involved in such decisions to enhance medicines self-care.

These lists focus on high risk medicines but many AEs and side effects are due to commonly prescribed and self-prescribe medicines, not on lists such as BEERS. Miller et al. [40] reported 11.6% of people had at least one AE in the preceding six months, most of which were mild to moderate; 11.8 were severe and 5.4% required a hospital admission as a result of using 13 commonly prescribed medicines not on lists such as BEERS Criteria [15,16]. These tools were developed to aid medicine prescribing decisions, not replace reasoned clinical decision-making. However, STOPP does help identify possibly avoidable AEs [41]. Some decision support tools are not appropriate for every country because they list medicines not commonly used or available in some countries [37].

## Conclusion

Enhancing the knowledge and competence of health professionals, older people with diabetes and other careers responsible for managing medicines with/for older people is essential [3,4,5]. Health professionals responsible for managing older people with diabetes must understand the pharmacology of, warnings about and contraindications to commonly used GLMs and where to access reputable medicines information.

They must also be alert to the emerging importance of diabetes-related cognitive change and mood disturbances that have profound effects on adherence to treatment and the ability to achieve safe, effective targets. Many health and social care professionals also provide care for frail vulnerable older people; thus, it is reasonable to suggest that understanding the concept of frailty could help optimise prescribing for older people. Incorporating frailty measures into future clinical studies of medicine effects and pharmacokinetics is important if we are to improve medication use and guide medicine doses appropriate for frail older people [43].

Older people have often lived with their diabetes for many years and are 'experts in their diabetes', consequently many functionally independent older people want to be involved in care decisions [44].

Personalized medicine education is more effective than 'standard' education that does not take account of the individual's personal risk factors, literacy level and other needs and/or the needs of family and other careers. There are many reputable on-line sources of information as well as phone apps that can help people manage their diabetes and medicines safely. Generally a combination of written and verbal information is desirable [45].

It is important to identify individual factors that lead to medicine non-adherence such as polypharmacy, misinterpreting medicine side effects, not understanding the 'directions for use,' medicine beliefs and attitudes, costs, and access. Tools such as the Brief Medicine Questionnaire, Medicine Adherence Report (MARS) and the Beliefs about Medication Questionnaire (BaMQ) [4]. The Morisky Medication Adherence Scale [46] can be used to determine non-adherence but it has low validity and uses judgemental language.

QUM and pharmacovigilance have their basis in ethical patient care. Health professionals have a duty of care to deliver safe, ethical care and 'first do no harm.' Ensuring the environment in which health professionals manage medicines has relevant infrastructure to actively support patient safety generally and for medicines in particular. The infrastructure should include accessible medicine guidelines and policies in place to support pharmacovigilance. For example, automated alerts to medicine allergies, hypoglycaemia risk, CAM medicine use, and prescribed HRMs. Currently, hypoglycaemia risk and CAM use are not standard medicine alerts. Medicine lists for people with diabetes can be helpful if they are kept current and communicated among health professionals caring for the individual, especially prescribers. Usually a combination of methods is more effective than single strategies [45].

It is more difficult to identify health professional-related factors that lead to inappropriate prescribing. Some factors include inadequate communication multiple prescribers, knowledge deficits and ageist attitudes. Older physician are less likely to follow guidelines or prescribe newer medicines for various reasons [46]. It is likely these traits also occur in other health professional disciplines.

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