Review of Medication in Patients with Dementia

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List of Abbreviations

AChEI	Acetylcholinesterase inhibitor
AGS	American Geriatrics Association
ATC	Anatomical Therapeutic Chemical Classification System
BZD	Benzodiazepines
CNS	Central nervous system
eGFR	Estimated glomerular filtration rate
NSAID	Non-steroidal anti-inflammatory drug
PIM	Potentially inappropriate medication
PIP	Potentially inappropriate prescribing
SSRI	Selective serotonin reuptake inhibitor
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions

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K. S. Frederiksen, G. Waldemar (eds.), *Management of Patients with Dementia*,
https://doi.org/10.1007/978-3-030-77904-7_6

Introduction

Physicians have access to potent drugs, which represent an important and common form of treatment. Prescribing medication is a longitudinal process that stretches from the initial decision to write a prescription and increasing the dosage to lowering it and making the choice to stop the medication. During this journey many opportunities arise to review the drug therapy in a structured way, e.g. during the work-up for cognitive impairment or dementia.

Many drugs can lower cognitive ability, typically those with anticholinergic effects but also ones that specifically target the central nervous system (CNS), for example antiepileptic drugs may have unwanted effects on cognition. Taking this into account is especially important when investigating older adults who simultaneously take many different drugs and have reduced cognitive reserve.

As a result, acquiring an accurate drug history is important during the work-up for cognitive impairment. In patients with cognitive disorders the history needs to be supplemented by relatives, other caregivers and by reviewing medical records. When addressing compliance, any drugs prescribed must be compared with the medicines that patient is taking. Equally important, non-prescription over-the-counter drugs and nutritional supplements that the patient uses must be considered. Quickly obtaining information about who the person with the most up-to-date knowledge on the patient's medical history is valuable, especially if the patient lives alone. The next imperative step is to ensure that patient consent is provided to obtain information from other sources. When setting up an appointment, it is advisable to ask the patient (or caregiver) in advance to bring a medication list to the appointment and, if possible, the actual packages. Any differences in terms of the actual current drug use can then be discussed during the patient's visit. Often well-received by patients, dose dispensing systems are increasingly available in many countries (Fig. 6.1).

Not only is the type of drug but also dosage important. The most common drug-related problem in older adults is prescribing a dose that is too high, with older

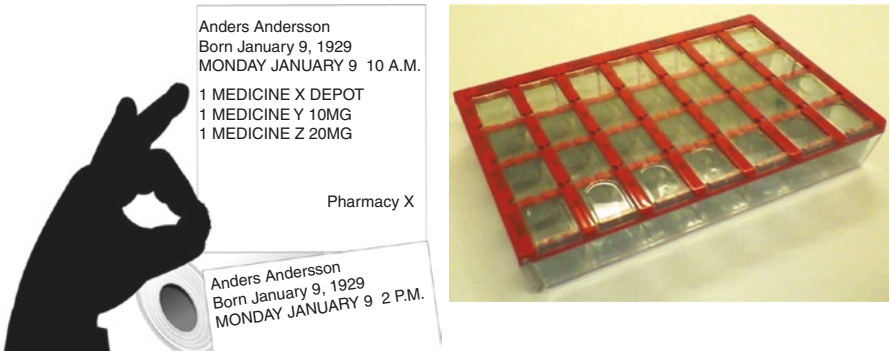

Fig. 6.1 Dose dispensation bags and convenient medicine boxes are often helpful tools for patients with memory problems, especially when compliance is an issue

adults possibly responding with side effects to doses recommended for younger patients.

Since age is the most important risk factor for dementia, it must also be taken into account in terms of problems related to drug treatment. With increasing age, both the body's ability to absorb, distribute, convert and secrete drugs (pharmacokinetics) and its sensitivity to drugs (pharmacodynamics) change.

In the following some of the drug-related problems that need special consideration are described that can occur in patients with cognitive impairment.

Lack of Follow-Up

It is not uncommon that drug treatment is not followed up on in patients with cognitive problems. Patients can experience side effects, or the drug may be ineffective because the dose is not appropriate. Start low, go slow is an essential rule of thumb in older adults when scheduling follow-ups for increasing the dose, but it must be kept in mind that a drug can become ineffective if the patient stays on a lower dose for too long. For instance, a 68-year-old female patient diagnosed with depression and mild cognitive impairment after a memory work-up was prescribed an antidepressant. During the one-year follow-up at a memory clinic, she clearly had mild dementia. Unfortunately, the follow-up on the depression medication was not appropriate because the patient had not visited her primary care doctor enough in between. This example highlights the critical issue that patients with cognitive impairment or dementia may not seek out medical attention on their own but need a pre-scheduled appointment and that medical staff should actively ensure compliance, e.g. telephone consultation with a nurse.

Doing a medication review is essential from a medical perspective. Many countries have enacted legislation regulating regular medication reviews that puts the responsibility for medication (e.g. writing prescriptions) on the physician [1] and, if necessary, in collaboration with other healthcare professionals. Emphasising patient involvement is also important and differs from patient consent. Physicians must familiarise themselves with the patient's current medication and systematically discuss the therapy and therapeutic options with the patient using suitable tools. In Sweden patients 75 years of age or older taking at least five prescription medications must be given a patient medication review at visits to outpatient doctors, during inpatient enrolment, home care visits, when moving to a nursing home and yearly if receiving home care or when living in a nursing home, but also when drug-related problems exist or are suspected [2].

In some countries, pharmacists are available for consultation but are not usually a mandatory part of a medication review. However, in some locations, pharmacists play a crucial role in medication reviews, a practice reflected in the large share of recently published articles on medication reviews written by clinical pharmacists. Regardless, it is important to decide on the division of tasks in a medication review and to conduct the follow-up as early as possible and if feasible, especially when a patient is cognitively impaired.

A systematic review of medicines management issues in dementia [1] identified challenges and solutions to medication management described by people with dementia and their carers. A common issue was a worsening of the ability to plan, organise and execute medicine management tasks. Additional related issues were forgetfulness, confusion and lack of insight. A proposed solution was accepting assistance with medication and transferring responsibility for medicine management to the family carer. However, the review showed that sometimes caregivers can be forgetful themselves, which is why it is also important to assess the ability and resources of the family caregiver before delegating the responsibility. Other solutions for dealing with reduced organisational abilities were visual aids and/or external memory reminders such as diaries, alarms and activity planners. The review also pointed out that risk of medication errors (e.g. under/overdose) was an issue, especially when new medications are introduced. Medicine aids [pill box (Fig. 6.1)] represent a possible solution, just as internal and external memory strategies can be helpful, for instance by linking to the patient's daily routine. Difficulties in maintaining a continuous supply of medicine was another issue, but one that could possibly be solved by sending/faxing prescriptions from the hospital to the pharmacy and the patient's home, using online prescription systems, home delivery of medications and simplifying dosing regimens. The review also pinpointed stress caused by non-professional care responsibilities as an issue for carers, but one that the temporary replacement of the carer could ameliorate. The review indicated that family caregiver communication with healthcare professionals was important and played a role in giving medications safely, recognising side effects and increasing preparedness on how to deal with medication-related emergencies.

Prescribing Cascade

The prescribing (or prescription) cascade is an undesirable sequence of events that begins when the drug is prescribed and a side effect occurs that is misinterpreted as a new medical condition, causing another drug to be prescribed to treat this condition. In the memory clinic setting a very commonly occurring prescribing cascade in the memory clinic setting is antipsychotic → parkinsonism → antiparkinsonian drug therapy. Another common cascade links the initiation of a non-steroidal anti-inflammatory drug to the development of hypertension and subsequent initiation of antihypertensive therapy [2]. A recent study also carefully examined a common cascade that occurs when older adults with hypertension are newly prescribed a calcium channel blocker and then subsequently given a loop diuretic at higher rates than those who began taking other antihypertensive medications [3] due to oedema misinterpreted as a new medical condition. An obvious way to prevent prescription cascades that should be kept in mind during medication review in dementia is alternative treatment strategies such as non-pharmacological treatment, e.g. for pain.

After a dementia diagnosis, newly prescribed acetylcholinesterase inhibitors (AChEIs) can result in sudden worsening of urinary incontinence, a new

problem often treated with anticholinergic drugs (e.g. oxybutynin chloride, tolterodine tartrate and flavoxate hydrochloride), resulting in what can be considered a prescribing cascade. A Canadian study showed that older adults with dementia on AChEIs had a 1.55 times higher risk of being subsequently prescribed an anticholinergic drug for urinary incontinence compared to older adults with dementia not on AChEIs [4]. Dementia patients taking donepezil and an anticholinergic drug had worse cognitive outcomes at 2 years, showed a seven-point decline in the Mini-Mental State Examination score compared to a two-point decline in patients taking donepezil only [5]. However, not all studies found that cognition or function worsened with the AChEI-anticholinergic combination [6]. A recent meta-analysis reported that anticholinergic drug use is associated with increased dementia and cognitive decline, but causation has not yet been confirmed [7]. The aforementioned Canadian dataset, with data from 1.8 million older adults, which allowed the identification of a link between use of cholinesterase inhibitor therapy to initiation of urinary anticholinergics [4], also showed a prescription cascade with lithium use and that treatment for parkinsonism began later [8].

The path to reducing **prescribing cascades** should include prevention, detection and reversion. The best strategy for reversion of prescription cascades is to ask what the indication for this drug is, in addition to providing education about de-prescribing and dose-tapering strategies. Other available resources to reduce cascades include detection algorithms, protocols, games [9] and checklists [2]. Case reports also represent a highly illustrative method, e.g. dose reduction to reverse rhinorrhoea after starting AChEI treatment [10].

Polypharmacy

In polypharmacy, defined as the use of multiple [5–10] medications, with >10 known as excessive polypharmacy, the risk of drug side effects increases exponentially. The most important risk factor for side effects is the number of drugs used. The risk of drug interactions also increases exponentially. At the same time, adherence to drug prescriptions diminishes, presenting the risk that patients will neglect the most important drugs.

In a recent analysis with data from 18 countries, the prevalence of polypharmacy in older adults (although mostly without dementia) was 26.3% to 39.9% [11]. A recent Danish study in a dementia population showed that, from 2011 to 2014, the prevalence of polypharmacy decreased negligibly from 69.4% to 68.1% in people with dementia and from 36.1% to 35.2% in people without dementia [12]. Polypharmacy in patients with dementia is associated with an increased risk of visiting the emergency department, hospitalisation and death, as the risk of any or unplanned hospitalisation may increase by 12% in those taking 4–6 medications, with a dose-response relationship between number of medications and adverse health outcomes [13].

Potentially Inappropriate Medications

The American Geriatrics Society (AGS) Beers Criteria® defines potentially inappropriate medications (PIMs) as medications that should generally be avoided in people 65 years or older because they are either ineffective, pose an unnecessarily high risk for older people and a safer alternative is available. One study showed an independent association between PIM use and dementia (odds ratio 1.69) [14], the authors suggesting that identifying inappropriate medication use can help prevent, delay and reduce PIM use and related adverse health outcomes.

De-prescribing

Physicians in a memory clinic setting must be willing to de-prescribe medications that are inappropriate, even if they are not the main prescriber for most of them. The best way to approach de-prescription is in dialogue and agreement with other physicians, though with one of them taking responsibility for initiating the discussion and de-prescription. A crucial issue for hospital-based physicians is to get the general practitioner on board. Other obstacles can be family caregivers and professional caregivers who might be concerned that de-prescription may lead to the re-emergence of symptoms. As a result, shared decision making and setting goals with adequate follow-up, for instance a contact number for the patient or caregiver to use in case of re-emergence of symptoms, may be useful.

Review of Drugs in Patients with Advanced Dementia

Dementia is an age-associated morbidity that ultimately becomes a life-defining illness. As such, when the disease unavoidably progresses, the goal of treatment shifts towards promoting quality of life and reducing the burden of pharmacotherapy to the greatest extent possible. It has been shown that patients with advanced dementia are at greater risk of receiving aggressive pharmacotherapy, which may not align with the proper goals of treatment but, at the same time, these patients may be experiencing physical and psychological symptoms, including agitation, depression, pain and constipation. Hence, they may significantly benefit from appropriate pharmacotherapy at the end of life. As a result, the goal of the treatment at the end of life is to reduce unnecessary pharmacotherapy and introduce other more suitable drugs, i.e. ones that reduce symptoms rather than prevent future illnesses. Examples of the drugs used, which may be referred to as essential in palliative care, are antidepressants, analgesics and laxatives.

Kidney Function

As decreased kidney function is a feature of normal aging, chronic kidney disease is common in older individuals. In all patients with renal abnormalities, the adjustment of drug doses is an essential issue in all those who are treated with nephrotoxic

drugs or drugs removed by the kidney. Furthermore, there are drug combinations which may be harmful to the kidney, e.g., they may increase the risk of pre-renal kidney injury: a combination of non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, ACEI or ARB (angiotensin receptor blockers) [15]. In patients treated with any harmful combinations, adding a drug that worsens kidney function may be dangerous. Consequently, to avoid the side effects of drugs that may negatively impact kidney function, it is imperative to calculate the estimated glomerular filtration rate (eGFR) based on creatinine level, bearing in mind that eGFR can easily change when the water balance is altered (e.g. less fluid intake and vomiting). Thus, in patients with an unstable clinical condition, a current eGFR value is needed.

A list of drugs with prescription recommendations for patients with an eGFR below 30 ml/min/1.73 m^2 can be compiled based on updated AGS Beers Criteria® [16] and consensus guidelines for oral dosing of primarily renally cleared medication in older adults [17] and include the following neuropsychotropic drugs:

- duloxetine—avoid
- venlafaxine—reduce dose
- gabapentin—reduce dose
- levetiracetam—reduce dose
- pregabalin—reduce dose
- topiramate—reduce dose
- memantine—reduce dose
- piracetam—reduce dose
- risperidone—reduce dose
- sulpiride—reduce dose

Every drug description included information on how to dose according to kidney function and helpful reminders. Today, the most important step is to integrate the kidney function and electronic advice on dosage. In some countries the prescription module in electronic patient records is integrated with renal status (eGFR), leading to an increase in follow-up on patients and concrete suggestions for drug reduction as renal function/dysfunction may have some merits.

Potentially Inappropriate Prescribing

Potentially inappropriate prescribing (PIP) is defined as the use of medicines that pose more risk than benefits, especially when safer alternatives exist, and mainly involves medications that should generally be avoided in older populations. The risk of PIP varies from patient to patient, though patients with dementia are particularly sensitive to PIP due to the spectrum of drugs used to treat them.

Literature reviews show that the prevalence of PIP in dementia varies significantly between studies due to their high level of clinical heterogeneity [18]. It is safe to assume, however, that PIP occurs in one third of community dwelling individuals (the lowest value identified by a study focusing on individuals with mild dementia only), and in even every other resident in nursing homes/specialised care homes [19].

Two types of PIP in patients with dementia can be distinguished [20]. The first one results from a more frequent application of medicines like benzodiazepines (BZDs), antidepressants, neuroleptics in patients with dementia than in the general population because these medications are used to control various behavioural and psychological symptoms common in dementia (e.g. aggression, wandering and sleep disturbances). They often pose more risk than benefit due to narrow therapeutic indices. The second type of PIP emerges from medications used in the treatment of comorbid medical conditions. As dementia is frequently accompanied by comorbidities, they are often managed with multiple medications that lead straight down a path to polypharmacy, which itself creates the risk of both adverse drug reactions and thus PIP. Based on a literature review, Parsons [21] reported that people with dementia take an average of 5–10 medications, one to two of which are prescribed because of dementia, the remaining ones indicated for treating other comorbid conditions. Although polypharmacy is a significant risk factor of PIP [22], it is not always inappropriate by itself but contributes to the complexity of managing the possible side effects of every medication and the potential consequences of drug interactions.

PIP is always related to adverse drug reactions, which are an unwanted, undesirable effect of a medication that occurs during typical clinical use. Cognitive impairment contributes to the substantially higher prevalence of adverse drug reactions, mainly due to nonadherence. Patients with cognitive impairment may not follow their medication regimen, forgetting to take their medication or taking it inappropriately. Notably, the risk of medication nonadherence increases with a higher number of drugs, further increasing the risk of adverse drug reactions.

Multiple tools are available to help identify PIP, but most of them are designed with older adults in mind and not specifically tailored to dementia. Even though this is the case, the tools contain items that can be applied to the review of medication in patients with dementia. These three tools are used most widely:

- AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older adults [16]
- Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) [23, 24]
- PRISCUS list [25]

AGS Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older adults

These criteria, which have been in common use for 30 years worldwide, not only by physicians but also by other professionals [26], provide a list of PIM that should be avoided in older patients in most situations but also certain circumstances and in specific conditions. Many countries have incorporated the list into their electronic medical record systems so that the physician receives a warning when the drug is prescribed for people over the age of 65 or 75 years, for example. Since 2011, AGS

has updated the criteria every 3 years. For the last update (2019), a multidisciplinary expert panel examined the evidence published since the previous update (2015) to verify whether new criteria were necessary, or whether existing criteria were still valid or needed changes (in terms of their rationale, level of evidence or strength of recommendations). The current AGS Beers Criteria® is the third update by AGS and the fifth since the original release. The criteria include a list of drugs that are strongly recommended to be avoided in older individuals. Among them are drugs that negatively effect on the CNS:

1. *Anticholinergics*, due to high risk of confusion (quality of evidence: moderate): first-generation antihistamines: brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine (oral: use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate), doxylamine, hydroxyzine, meclizine, promethazine, pyrilamine, triprolidine
2. *Antispasmodics*, as they are highly anticholinergic and their effectiveness is uncertain (quality of evidence: moderate): atropine (excludes ophthalmic), belladonna alkaloids, clidinium-chlordiazepoxide, dicyclomine, homatropine (excludes ophthalmic), hyoscyamine, methscopolamine, propantheline, scopolamine
3. *CNS alpha-agonists*, due to high risk of adverse effects on the CNS (quality of evidence: moderate): clonidine for first-line treatment of hypertension, other CNS alpha-agonists: guanabenz, guanfacine, methyldopa, reserpine (>0.1 mg/day)
4. *CNS antidepressants*, alone or in combination due to their highly anticholinergic effect (quality of evidence: high): amitriptyline, amoxapine, clomipramine, desipramine, doxepin >6 mg/day, imipramine, nortriptyline, paroxetine, protriptyline, trimipramine
5. *Antipsychotics (first (conventional) and second (atypical) generation)*, due to increased risk of cerebrovascular accident (stroke) and a greater rate of cognitive decline and mortality in persons with dementia; should be avoided for behavioural problems in dementia or delirium unless non-pharmacological options (e.g. behavioural interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others (except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy) (quality of evidence: moderate)
6. *Barbiturates*, due to high rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages (being phased out in many European countries)
7. *BZDs*, all of which increase the risk of cognitive impairment, delirium (may be appropriate for seizure disorders, rapid eye movement sleep behaviour disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalised anxiety disorder, periprocedural anaesthesia (quality of evidence: moderate): short- and intermediate-acting: alprazolam, estazolam, lorazepam, oxazepam, temazepam, triazolam; long-acting BZDs: chlordiazepoxide (alone or in combination with

amitriptyline or clidinium), clonazepam, clorazepate, diazepam, flurazepam, oxazepam
8. *Meprobamate*, due to high rate of physical dependence and sedating (quality of evidence: moderate)
9. *Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (i.e. Z-drugs)*, due to their adverse events (e.g. delirium), which are similar to those of BZDs in older adults and include increased emergency room visits/hospitalisations, minimal improvement in sleep latency and duration (quality of evidence: moderate): eszopiclone, zaleplon, zolpidem

The 2019 AGS Beers Criteria® also comprises a list of drugs that are discouraged in certain clinical conditions due to drug–disease or drug–syndrome interactions. Among them there are drugs which may exacerbate:

1. *May exacerbate dementia and cognitive impairment:*
   (a) Anticholinergics (quality of evidence: moderate)
   (b) BZDs (quality of evidence: moderate)
   (c) Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics: eszopiclone, zaleplon, zolpidem (quality of evidence: moderate)
2. *May exacerbate* delirium:
   (a) Anticholinergics (quality of evidence: moderate)
   (b) Antipsychotics (quality of evidence: moderate)
   (c) Benzodiazepine (quality of evidence: moderate)
   (d) Corticosteroids (oral and parenteral) (quality of evidence: moderate)
   (e) H2-receptor antagonists (cimetidine, famotidine, nizatidine, ranitidine, meperidine) (quality of evidence: low)
   (f) Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics: eszopiclone, zaleplon, zolpidem (quality of evidence: moderate)

Note that, due to weak supporting evidence, the most recent AGS Beers Criteria® update removed H2-receptor antagonists from the "avoid" list of drugs that can potentially affect the CNS in patients with dementia or cognitive impairment. This criterion, combined with another one that de-recommends chronic use of proton pump inhibitors without strong indications, could have severely restricted the therapeutic possibilities for older individuals with dementia and gastroesophageal reflux or similar conditions. H2-receptor antagonists remain, however, on the "avoid" list for patients with delirium.

STOPP/START

In 2003, due to the limitations of existing criteria (including the AGS Beers Criteria®, which had some deficiencies, e.g. several listed drugs were not available in Europe or were not contraindicated), a European panel of experts reached a consensus

based on a literature review and validation discussions, leading to the publication of the two-part STOPP/START criteria [27]. STOPP lists drugs to be avoided due to their potential inappropriateness in older persons and START lists drugs frequently omitted in prescriptions but that should be considered for older patients where no contraindications exist. The STOPP part also includes drugs that adversely affect older patients at risk of falls, analgesics and duplicate drug class prescriptions (e.g. two angiotensin converting enzyme inhibitors or two proton pump inhibitors). In both tools, drugs were grouped by physiological systems (e.g. the cardiovascular system or CNS), making their use easier.

A group of experts in geriatric medicine, clinical pharmacology, clinical pharmacy, old age psychiatry and primary care subsequently validated the STOPP/START criteria in 2006. These experts were also invited to suggest additional criteria that were not included in the original drafts of STOPP/START. They finally agreed on a list of 65 STOPP and 22 START criteria (STOPP/START version 1).

In 2015, following expansion of the therapeutics evidence base, a thorough literature review was performed to reassess the 2008 criteria and create a new version, in accordance with the same rules as previously (STOPP/START version 2).

The 2015 STOPP list [24] mentions dementia twice, which means that two groups of drugs should be avoided in patients with dementia. Among the central nervous system drugs there are tricyclic antidepressants (due to the risk of worsening cognitive impairment) and among urogenital system drugs—the bladder antimuscarinic drugs (due to the risk of increased confusion and agitation). The previous STOPP lists (2003/2006) contained analgesics, also long-term opioids, due to the risk of exacerbation of cognitive impairment, unless indicated for palliative care or management of moderate/severe chronic pain syndrome. They were removed from the 2015 list as the evidence was weak.

The STOPP criteria also include, however, drugs that should be used with caution in patients with dementia. The reason suggested for avoiding them is related to potentially harmful CNS effects:

- Long-term (>1 month), long-acting BZDs, e.g. chlordiazepoxide, flurazepam, nitrazepam, clorazepate and BZDs with long-acting metabolites, e.g. diazepam (risk of prolonged sedation, confusion)
- Long-term (>1 month) neuroleptics like long-term hypnotics (risk of confusion, hypotension, extrapyramidal side effects)
- Anticholinergics to treat extrapyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity)
- Prolonged use (>1 week) of first-generation antihistamines, e.g. diphenhydramine, chlorpheniramine, cyclizine, promethazine (risk of sedation and anticholinergic side effects)

The START list is limited to the general population of older individuals and does not mention patients with dementia or cognitive impairment.

PRISCUS List

The history of the PRISCUS list is similar to that of the STOPP/START criteria. International recommendations regarding the correct treatment of older patients, particularly those with multimorbidities, were difficult to apply in Germany because they often did not apply to the situation in German because of differences in which drugs are approved, prescribing behaviour and therapeutic guidelines. The project, named PRISCUS, which is Latin for old and frail, was dedicated to PIM for older patients in the German-speaking countries. The PRISCUS list includes drugs whose use in older adults carries an increased risk of adverse drug events. The list was put together after a review of existing lists from other countries and a review of the current literature. This list has not been updated since its inception, but it has the significant advantage that possible therapeutic alternatives are indicated for each PIM.

The PRISCUS list contains 83 PIMs, which includes drugs that can potentially affect the CNS or that should be used with caution in patients with cognitive impairment. The following items only indicate how they act on the CNS:

1. Non-steroidal anti-inflammatory drugs: indomethacin, due to central nervous disturbances; possible alternatives are: paracetamol, weak opioids (tramadol, codeine) and weak NSAIDs (e.g. ibuprofen)
2. Opioid analgesics: pethidine, due to elevated risk of delirium; possible alternatives are: paracetamol, other opioids (with lower risk of delirium, e.g. tilidine/naloxone, morphine, oxycodone, buprenorphine, hydroxymorphone) and weak NSAIDs (e.g. ibuprofen)
3. Antiarrhythmic drugs:
   (a) quinidine, due to CNS side effects; possible alternatives are: beta blockers, verapamil, diltiazem, amiodarone, defibrillator implantation
   (b) flecainide, due to higher rate of adverse effects, CNS effects (e.g. vertigo, cognitive impairment) should be monitored; possible alternatives are: beta blockers, amiodarone
4. Anticholinergic drugs due to impaired cognitive performance:
   (a) Antihistamines: hydroxyzine, clemastine, dimetindene, chlorpheniramine, triprolidine; possible alternatives are: non-sedating, non-anticholinergic antihistamines (e.g. cetirizine, loratadine, desloratadine)
   (b) Urological spasmolytic agents: oxybutynin (non-sustained-release and sustained-release formulations), tolterodine (non-sustained-release), solifenacin; possible alternatives are: trospium, non-pharmacological treatment (e.g. pelvic floor exercises, physical and behavioural therapy)
5. Antidepressants:
   (a) Tricyclic antidepressants (amitriptyline, doxepin, imipramine, clomipramine, maprotiline, trimipramine), due to central anticholinergic side effects (e.g. drowsiness, inner unrest, confusion, other types of delirium) and cognitive deficit; possible alternatives are: Selective serotonin reuptake inhibitors (SSRIs) (e.g. citalopram, sertraline), mirtazapine, non-pharmacological treatments such as behavioural therapy

   (b) Among SSRIs: fluoxetine, due to CNS side effects (e.g. insomnia, dizziness, confusion), hyponatraemia; possible alternatives are: another SSRI (e.g. citalopram, sertraline), trazodone, mirtazapine, non-pharmacological treatments such as behavioural therapy
   (c) Monoamine oxidase inhibitors: tranylcypromine, due to risk of cerebral haemorrhage; possible alternatives are: SSRIs (other than fluoxetine), non-pharmacological treatments such as behavioural therapy
6. Antiemetic drugs: dimenhydrinate, due to anticholinergic side effects; possible alternatives are: domperidone, metoclopramide (beware of extrapyramidal side effects)
7. Antihypertensive agents and other cardiovascular drugs: Clonidine, due to CNS side effects (sedation, cognitive impairment); Alpha blockers (doxazosin, prazosin, terazosin (as an antihypertensive agent), due to CNS side effects (e.g. vertigo, light-headedness, somnolence), increased risk of cerebrovascular disease; Methyldopa, due to sedation; Reserpine due to CNS effects (sedation, depression). Possible alternatives are: other antihypertensive agents, e.g. angiotensin converting enzyme inhibitors, AT1 receptor blockers, thiazide (diuretics), beta blockers, calcium antagonists (long-acting, with peripheral effect)
8. Neuroleptic drugs: Classic neuroleptic drugs: thioridazine, fluphenazine, levomepromazine, perphenazine, haloperidol (>2 mg); Atypical neuroleptic drugs: olanzapine (>10 mg), clozapine. The main concerns are anticholinergic and extrapyramidal side effects, parkinsonism, sedation, falls and increased mortality in patients with dementia; fewer extrapyramidal side effects when atypical neuroleptics are used; possible alternatives are neuroleptics of low potency (e.g. melperone, pipamperone) or atypical neuroleptics with a favourable risk/benefit profile (e.g. risperidone)
9. Muscle relaxants: baclofen, tetrazepam due to CNS effects: amnesia, confusion; possible alternatives for baclofen are: tolperisone, tizanidine, physical therapy; for tetrazepam: short/intermediate-acting BZDs in low doses
10. BZDs, due to psychiatric reactions (sometimes paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment, depression, increased risk of falls (excluding depression for Z-drugs).
    (a) Long-acting BZDs: chlordiazepoxide, diazepam, flurazepam, dipotassium clorazepate, bromazepam, prazepam, clobazam, nitrazepam, flunitrazepam, medazepam
    (b) Short-/intermediate-acting BZDs (alprazolam, temazepam, triazolam, lorazepam (>2 mg/d), oxazepam (>60 mg/d), lormetazepam (>0.5 mg/d), brotizolam (>0.125 mg/d)
    (c) Z-drugs: zolpidem (>5 mg/d), zopiclone (>3.75 mg/d), zaleplon (>5 mg/d)

Possible alternatives for long-acting BZDs are short-/shorter-acting benzodiazepines, Z-drugs (a low dose), opipramol, sedating antidepressants (e.g. mirtazapine), neuroleptic drugs of low potency (e.g. melperone, pipamperone); for short-/intermediate-acting and Z-drugs: valerian, sedating antidepressants (trazodone, mianserin, mirtazapine), opipramol, low-potency neuroleptic drugs (melperone, pipamperone), non-pharmacological treatment of sleep disturbances (sleep hygiene); for short-/intermediate-acting BZDs: zolpidem (≤5 mg/d).

11. Other sedative agents:
    (a) Doxylamine, diphenhydramine due to anticholinergic effects and dizziness; possible alternatives are the same as for short-/intermediate-acting BZDs
    (b) Chloral hydrate due to dizziness

Possible alternatives for both listed above are the same as for short-/intermediate-acting BZDs.

12. Other antiepileptic drugs: phenobarbital, due to sedation and paradoxical excitation; possible alternatives are other antiepileptic drugs: lamotrigine, valproic acid, levetiracetam, gabapentin

Possible Cognitive Side Effects of Major Drug Classes

This section provides a list of the major classes of drugs in the Anatomical Therapeutic Chemical Classification System (ATC) that have cognitive side effects and a brief description of their side effects, with a focus on elderly people with dementia. This list can aid in assessing possible cognitive side effects of a particular drug during a medication review for patients with dementia.

Cognitive effects are seen not only in drug treatment affecting the CNS [28–30] but may also occur in electrolyte balance disorders [29], for example in diuretics treatment. Anticholinergic effects are found in many different drug groups, such as antihistamines, anti-incontinence drugs and tricyclic antidepressants. The degree of anticholinergic effect of the drugs varies and the overall anticholinergic effect should be taken into account rather than the anticholinergic effect of individual substances. Scales are available for estimating a patient's total anticholinergic load that can be of help in the medication review. Drugs less known for their potential anticholinergic activity are digoxin, amantadine, prednisolone, metoprolol, warfarin and morphine

Individual Assessment

Some patients are more sensitive than others to the side effects of drugs, which is why individual assessment is necessary, even if studies do not show impairment or impairment cognitive function

Below is a selected list of drugs with their ACT code and a brief description of how they act. The first level of each code indicates the anatomical main group, of which there are 14, and consists of one letter. The groups listed below include: 'A', which stands for alimentary tract and metabolism; 'G', which stands for genito-urinary system and sex hormones; 'M', which stands for musculo-skeletal system; and 'N', which stands for nervous system. The second level comprises two digits and indicates the therapeutic subgroup, while the third level indicates the therapeutic/pharmacological subgroup and comprises one letter

A04 Antiemetics

Serotonin receptor antagonists do not appear to affect cognition in a negative direction, while scopolamine exhibits clear anticholinergic and thus cognitive effects.

A10 Diabetes agents

Most importantly, hypoglycaemia may be an issue with antidiabetics, which may have adverse cognitive effects. Studies have shown that experimentally keeping blood glucose at 4.5 mmol/l in type 2 diabetes had a negative impact on process speed, memory and attention compared to blood glucose at 16 mmol/l [31]. The influence of hyperglycaemia is generally less than for hypoglycaemia [32] but some studies in blood glucose >20 mmol/l showed a potentially negative effect.

The American Diabetes Association has recently added three new recommendations on hypoglycaemia in the elderly, for instance: glycaemic goals can be relaxed in the older population as part of individualised care that focuses on individualised pharmacotherapy with glucose-lowering agents with a low risk of hypoglycaemia and proven cardiovascular safety [33].

Insulin therapy always carries a potential risk of severe hypoglycaemia, which gradually influences the cognitive function and results in the occurrence of diabetic coma. Since severe hypoglycaemia renders the individual unconscious, someone else must intervene to reverse it. Severe hypoglycaemia often refers to a fixed blood sugar level, often 2.8 mmol/L, but other values may occur.

Insulin therapy increases the risk of severe hypoglycaemia. In most studies, patient-reported hypoglycaemia symptoms are most often described and often hypoglycaemia is not verified with the measurement of blood/plasma glucose. In the studies examined, hypoglycaemia was usually confirmed at blood glucose <3.3 mmol/l, sometimes <2.2 mmol/l, the latter blood glucose sometimes considered severe hypoglycaemia. Metformin appears to have a low hypoglycaemia rate, comparable to placebo, in a larger study reported at 4.2% of all participants [34]. The newest drugs used in diabetes, used alone or in combination, have different risk levels in terms of hypoglycaemia.

Recommendation: Ensure that patients with dementia, carers and healthcare staff can monitor glucose level and detect signs of hypoglycaemia.

G04 Urological Agents

An overactive bladder is successfully treated with anticholinergic drugs, but cognitive impact is more likely with increasing age. Darifenacin does not appear to have any impact on cognitive function, which is fortunate considering its high efficacy.

A recent review article asserted that oxybutynin may impair cognition in the elderly. For this age group, darifenacin, trospium, solifenacin and tolterodine are considered to have little risk of CNS side effects, but caution is still warranted in dementia, especially for the last-mentioned compound [35]

Darifenacin 15 mg × 1 (slow release) does not affect cognitive function and is comparable to placebo regarding adverse effects on cognition. Single dose oxybutynin (5 and 10 mg) has been shown to result in impaired cognitive test results in seven out of 15 neuropsychological tests [36]. Slow-release oxybutynin (20 mg) affects cognition, especially memory, in the elderly when compared to placebo and darifenacin (15 mg) [37]. Studies on tolterodine are lacking, though a couple of case histories have been described with memory impairment [38] and confusion [39].

M01A NSAID

In general, single-dose NSAIDs do not appear to affect cognitive function, while both improved and impaired test results may be detected with longer term treatment. It is well known that NSAIDs may have effects on the CNS in overdose [40].

N01 Anaesthetics

A review by Wu et al. [41] showed that the risk of postoperative impairment in cognitive function did not differ between general anaesthesia and regional anaesthesia. The review also showed that especially elderly people were sensitive to postoperative cognitive dysfunction, which could persist for one week postoperatively in 26% of patients, in some cases for up to months.

N02 Analgesics

There are three key issues to be aware of when reviewing analgesics in patients with dementia in terms of cognitive side effects: (1) pain has been shown to affect reaction speed and other cognitive functions, which is why treating it adequately is essential; (2) opioids negatively impact cognitive function, especially upon initiation of the therapy (up to 2 weeks but highly dependent on the individual); and (3) a stable dose of opioids is better than short-term, extra doses. Also note that with morphine, it is important to start with short acting before moving on to long acting.

N03 Antiepileptics

The cognitive side effects of antiepileptics are more common, although less studied, in elderly patients. The cognitive influence of most antiepileptic drugs has been described, but discerning whether it is the effect of the disease or drugs is difficult, as attested to by how results differ considerably among studies. Risk of cognitive side effect differs between various antiepileptics, but valproate, phenytoin, clonazepam, clobazam and gabapentin should be given special attention. Sarkis et al. [42], who did a review of phase-III studies on newer drugs, found adverse reactions in

placebo patients (cognitive in 0–10.6%; fatigue in 2.5–37.7%), making the results difficult to interpret. However, dose-response relationships were found for most antiepileptics, except for brivaracetam and zonisamide (for cognitive side effects) and tiagabine, topiramate and zonisamide (for fatigue). Cognitive side effects were present in at least 5% more patients than placebo subjects for eslicarbazepine (high load), perampanel (high load), pregabalin (average and high load), tiagabine (high load), topiramate (average and high load) and vigabatrin (high load). About 3% had cognitive side effects with placebo or low drug load, but 5.8% with average drug load and 8.7% with high drug load. Levetiracetam is reported by some to improve cognition [43] and lamotrigine to relieve depression in patients with cognitive impairment, while phenobarbital and lamotrigine could worsen cognition, and levetiracetam and phenobarbital could worsen mood. Levetiracetam does not appear to reduce cognitive ability but can produce undesirable effects in terms of aggressiveness and impulsivity. Chapter 12 provides detailed information on antiepileptics.

When monitoring antiepileptic treatment in patients with cognitive problems that are known or suspected, it is important to observe cognitive abilities. Patients can be asked whether they experience cognitive problems and cognitive tests can be administered. When a cognitive side effect is suspected, modification of the treatment should be considered.

N04 Anti-Parkinson Drugs

Cognitive function may be affected already in the early stages of the disease. For elderly patients with cognitive impairment it is important to choose medication that does not have a sedative effect (or as little as possible) and that does not contain an anticholinergic component. L-DOPA, also called levodopa, appears to be the best option. Selegiline and tolcapone seem to have the potential to improve cognition, and rasagiline seems to be neutral from a cognitive point of view.

N05A Neuroleptics

Clozapine appears to have less impact on cognitive function than other neuroleptics, but its anticholinergic effects may have significance, at least for elderly patients.

N05C Hypnotics and Sedatives

In some countries, half or more of patients with mild to moderate Alzheimer's disease were prescribed a sedative. Sedative load was associated with the risk of delirium and falls, which is why optimal prescribing is needed in individuals with Alzheimer's disease.

Recent evidence indicates that the use of BZDs and Z-drugs may be strongly associated with the risk of developing dementia [44]. Unfortunately, there is limited

evidence to aid in selecting pharmacotherapy for sleeping problems specifically for patients with dementia [45]. Recent studies examining the use of ramelteon and mirtazapine to treat sleep disorders in Alzheimer's disease showed they had no significant therapeutic effects. BZDs, the most common drugs for insomnia, may have significant side effects in older patients. The orexin receptor antagonist suvorexant was recently reported to be beneficial in insomnia in Alzheimer's disease [46]. Although melatonin is widely used because it has no side effects in people with dementia, studies on melatonin are very limited for this patient group.

Some hypnotics provide considerable effects on cognitive function measured using various neuropsychological tests. More long-acting hypnotics are found among BZDs, where nitrazepam, lorazepam, oxazepam and flunitrazepam have been studied.

N06A Antidepressants

Depression is a condition that requires special consideration in dementia (see Chap. 7). In one study, more than 20% of patients reported subjective cognitive symptoms in long-term treatment with SSRIs [47]. Tricyclic antidepressants initially have an impact on cognitive function, while paroxetine has some negative impact on it. Other antidepressants have varying degrees of influence and tolerance development, except venlafaxine and reboxetine, which seem to have no impact on cognitive function. SSRIs in dementia may be preferable, but depression itself may impair cognitive function.

Other Medicines and Electroconvulsive Therapy

A meta-analysis has shown that it is not possible to show impaired cognition in the long term measured with psychometric tests, but some patients experience a memory disorder long after electroconvulsive therapy. Cancer treatments such as radiation therapy and chemotherapy can also affect cognitive function. Moreover, subjective experiences of cognitive problems are common after chemotherapy, radiation treatment and other pharmacological treatments for cancer. Nootropics are an example of substances that claim to improve cognition, which is why asking patients about them is also relevant.

Other Issues

Non-cardiac drugs with proarrhythmic potential include antihistamines, selective serotonin reuptake inhibitors and AChEIs for dementia. Prolonged QT intervals (from the beginning of the QRS complex to the end of the T wave) can lead to life-threatening heart arrhythmias such as torsades de pointes. In recent years, donepezil and memantine have been known to increase the QT interval, resulting in sudden

cardiac death. Drug interactions can also lead to a cumulative effect on the QT interval [48]. To identify and prevent long QT intervals, calculating the QT interval has been suggested when elderly patients are treated for dementia [49]. Electronic resources, e.g. CredibleMeds®, are available to help avoid QT intervals that are too long.

Box 6.1 and 6.2 provide tips on doing the two main types of medication review; Table 6.1 is an example patient case.

Box 6.1 Patient Medication Review

Depending on how the clinic is organised, a physician, pharmacist or nurse speaks with the patient to secure a complete and accurate medication list. Checking with caregivers is important to know exactly which medications are used. Keep an eye out for pharmaceutical drugs with an unfavourable cognitive profile. Both cognition and other bodily functions should be optimised. Conducting a medication review in dementia often includes contacting physicians in other areas of medicine, e.g. urologists. Follow-up is always essential.

Electronic resources are often available for drug–drug interactions. For example, it is important to look for medications that prolong the QT interval of the electrocardiogram.

Based on documentation and the patient's own data identify:

- Drugs prescribed and why
- Strength and dose prescribed versus what is actually taken
- Non-prescription medicines, including over-the-counter drugs, herbal medicines and nutritional supplements
- If there are practical problems with the medicines and compliance

The physician will assess the effectiveness and safety of the drug treatment. Drug-related problems that can be readily solved should be addressed and, if a major drug-related problem is suspected, an in-depth medication review should be provided.

After the review:

- Update the drugs being used in the patient file
- Note the drug-related problems detected, measures taken, and follow-up planned
- Provide patient with individually tailored information on drug treatment and any actions taken
- Give the patient an updated list of medicines
- Give the patient a complete drug report once the patient is enrolled in inpatient care

Source: Modified based on Bergqvist M. and Segander, M. (2020) [50]

Box 6.2 Clinical Medication Review
An in-depth clinical medication review is based on:

- Updated list of medicines and other documentation from the patient medication review
- Estimation of symptoms, e.g. PHASE-20 1
- Test results, e.g. haemoglobin, sodium, potassium, creatinine, depending on the diagnoses and medicines
- Blood pressure (orthostatic if necessary), heart rate and weight
- Estimated glomerular filtration rate
- Interaction control, SFINX 2
- Declaration of any falls

A main goal of the clinical medication review is to identify potentially inappropriate drugs. Renal function and interactions are important. For each medicine:

- Check that there is an indication
- Evaluate the treatment effect based on treatment objectives
- Assess appropriateness of medication based on diagnoses, age, kidney function and other medicines
- Assess whether the dose is correct based on diagnoses, age, kidney function and other medicines
- Evaluate whether the drug's benefit is greater than its side effects or risk thereof
- Assess whether non-pharmacological alternatives or complement are available

For the drug treatment in its entirety:

- Check whether it follows current recommendations
- Assess whether the patient has problems taking action or understanding information
- Assess whether the patient can manage the drug treatment or has sufficient support to do so
- Assess whether undertreatment is present
- Check for clinically relevant interactions

After or during the clinical medication review:

- Update the patient file

- Note which medicines the patient uses
- Note the objectives of the drug treatment
- Indicate which drug-related problems have come to light and how to remedy them
- Note how and when to follow up, clearly indicating which healthcare provider/care unit is responsible for doing so
- Provide the patient with individually tailored information on measures taken and why; when and how to follow up; which healthcare provider/care unit is responsible for follow-up; and who participated in the review
- Give the patient an updated list of medicines

Source: Modified based on Bergqvist M. and Segander, M. (2020) [50]

Table 6.1 Patient case

Patient's story	Physician's view
Retired 67-year-old male who worked in sales in various countries; non-smoker, moderate alcohol intake. Uses a walker, pain problems starting from the right hip; surgery is planned. Lives alone but is in regular contact with sons and sister. Receives home care every morning and gets help once a week with his medicine box. Otherwise functions independently. Recently prescribed levodopa and benserazide for investigative reasons but says he does not feel any tangible effects from the drug. Although prescribed propiomazine at night he says today that he only takes one every 3 months. Has previously been informed of the risk of hangovers. Comments that he has accidentally taken a propiomazine instead of ibuprofen at one of the test sessions during his examination and believes this may have worsened his results. Seen in 2017 in a memory clinic for diagnostic evaluation. Neuropsychological testing showed impairments in various cognitive domains. Interpreting the findings was difficult due to a recent period of confusion caused by an orthopaedic injury. Dementia markers in the cerebrospinal fluid were all in the normal range. A component of neurodegeneration such as Alzheimer's, however, could not be excluded. Information about these conclusions given to relatives who seem to understand the content.	The physician notes that the patient has been drinking alcohol for years, a combination of wine and strong spirits. Intake estimated to be at least three bottles of wine weekly for several years, with a similar intake of whisky. The only break in alcohol consumption occurred after an accident and while patient admitted to a geriatric ward. Sleeps satisfactorily at night, has no depressive symptoms and maintains weight. Neurological status: rigidity, mostly on the right side; hypomimia; normal eye movements, no vertical gaze paresis; Romberg unremarkable; balance difficulties, uses a walker (due to hip problems). Referred to neurological specialist. Hand tremor of the parkinsonian type visible at later visit to the doctor's office, albeit weak; patient tries to downplay it. Cognition appears improved after initiation of anti-Parkinson drug.

Conclusion

Medication reviews are a method for mapping all of the drugs prescribed to and used by a patient and ensure an accurate and up-to-date list of medicines. The method also makes it possible to analyse, retest and follow up on a patient's entire medication use in order to detect, address and prevent drug-related problems.

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