














A European Academy of Neurology guideline on medical management issues in dementia

K. S. Frederiksen^a , C. Cooper^b , G. B. Frisoni^c , L. Frölich^d , J. Georges^e , M. G. Kramberger^f , C. Nilsson^{g,h} , P. Passmoreⁱ, L. Mantoan Ritter^j , D. Religa^{k,l} , R. Schmidt^m, E. Stefanovaⁿ , A. Verdelho^o , M. Vandenbulcke^p , B. Winblad^{q,l} and G. Waldemar^a 

^aDepartment of Neurology, Danish Dementia Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ^bDepartment of Clinical Educational and Health Psychology, University College London, London, UK; ^cMemory Clinic, University Hospital of Geneva, University of Geneva, Geneva, Switzerland; ^dDepartment of Geriatric Psychiatry, Zentralinstitut für Seelische Gesundheit Mannheim, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; ^eAlzheimer Europe, Luxembourg, Luxembourg; ^fDepartment of Neurology, Center for Cognitive Impairments, University Medical Center Ljubljana, and Medical faculty, University of Ljubljana, Ljubljana, Slovenia; ^gDepartment of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden; ^hClinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; ⁱQueens University, Belfast, UK; ^jEpilepsy Centre, King's College NHS Foundation Trust, King's College London, London, UK; ^kDivision of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Neo, Stockholm, Sweden; ^lKarolinska University Hospital, Theme Aging, Huddinge, Sweden; ^mUniversity Clinic for Neurology, Medical University of Graz, Graz, Austria; ⁿMedical Faculty, Neurology clinic CCS, University of Belgrade, Belgrade, Serbia; ^oDepartment of Neurosciences and Mental Health, CHLNorte-Hospital de Santa Maria, IMM, ISAMB, Faculty of Medicine, University of Lisbon, Lisbon, Portugal; ^pDepartment of Neurosciences, KU Leuven, Geriatric Psychiatry, University Hospitals Leuven, Leuven, Belgium; and ^qDivision of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, BioClinicum, Solna, Sweden

Keywords:

antipsychotics, dementia, epilepsy, follow-up, guideline, medical management, pain, vascular

Received 6 May 2020
revision requested 12 June 2020
Accepted 13 June 2020

European Journal of Neurology 2020, **27**: 1805–1820

doi:10.1111/ene.14412

Background and purpose: Dementia is one of the most common disorders and is associated with increased morbidity, mortality and decreased quality of life. The present guideline addresses important medical management issues including systematic medical follow-up, vascular risk factors in dementia, pain in dementia, use of antipsychotics in dementia and epilepsy in dementia.

Methods: A systematic review of the literature was carried out. Based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework, we developed a guideline. Where recommendations based on GRADE were not possible, a good practice statement was formulated.

Results: Systematic management of vascular risk factors should be performed in patients with mild to moderate dementia as prevention of cerebrovascular pathology may impact on the progression of dementia (Good Practice statement). Individuals with dementia (without previous stroke) and atrial fibrillation should be treated with anticoagulants (weak recommendation). Discontinuation of opioids should be considered in certain individuals with dementia (e.g. for whom there are no signs or symptoms of pain or no clear indication, or suspicion of side effects; Good Practice statement). Behavioral symptoms in persons with dementia should not be treated with mild analgesics (weak recommendation). In all patients with dementia treated with opioids, assessment of the individual risk–benefit ratio should be performed at regular intervals. Regular, preplanned medical follow-up should be offered to all patients with dementia. The setting will depend on the organization of local health services and should, as a minimum, include general practitioners with easy access to dementia specialists (Good Practice statement). Individuals

Correspondence: K. S. Frederiksen, Department of Neurology, Danish Dementia Research Center, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark (Tel.: +45 35456911; e-mail: Kristian.steen.frederiksen@regionh.dk).

with dementia and agitation and/or aggression should be treated with atypical antipsychotics only after all non-pharmacological measures have been proven to be without benefit or in the case of severe self-harm or harm to others (weak recommendation). Antipsychotics should be discontinued after cessation of behavioral disturbances and in patients in whom there are side effects (Good Practice statement). For treatment of epilepsy in individuals with dementia, newer anticonvulsants should be considered as first-line therapy (Good Practice statement).

Conclusion: This GRADE-based guideline offers recommendations on several important medical issues in patients with dementia, and thus adds important guidance for clinicians. For some issues, very little or no evidence was identified, highlighting the importance of further studies within these areas.

Introduction

An estimated 10.5 million people in Europe live with dementia, with the number expected to increase to 13.4 million in 2030 [1]. Many patients with dementia are elderly persons with comorbidities, such as cardiovascular conditions and diabetes, and also have an increased risk of developing epilepsy and behavioral symptoms. Opioids, anti-epileptic drugs (AEDs) and antipsychotics can worsen cognitive function in persons with dementia. Moreover, treatment with antipsychotics in this population is associated with an increased risk of cardiovascular accidents and mortality [2]. Inequality in access to physicians means that not all patients with dementia are offered systematic medical follow-up, and therefore treatable conditions may be overlooked or mismanaged, leading to accelerated functional decline, hospitalizations and increased mortality, and thus increased healthcare costs. Polypharmacy with adverse interactions and an unfavorable risk–benefit ratio is another frequent occurrence in this population, which requires systematic medical follow-up [3,4]. Moreover, for patients with dementia, treatment practices for associated medical conditions may vary due to uncertainty with regard to the balance between benefits and adverse effects, and due to a lack of scientific certainty.

The scope of the Guideline is to address pressing medical issues in patients with dementia typically managed by a medical doctor in both primary and secondary care sectors. Despite increasing focus on the underlying etiology of dementia and biomarker-based diagnosis [5,6], we have chosen to focus on the syndrome of dementia since many of the management issues are shared across disorders. Moreover, in a substantial number of patients, an etiological diagnosis may remain elusive. A number of European Academy of Neurology (EAN) and European Federation of

Neurological Societies guidelines exist on different aspects of diagnosis and treatment of dementia disorders [7–10], none of which overlap with the present Guideline.

The present Guideline is based on systematic reviews of the evidence and the use of Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [11] for the development of guidelines. Both are standard operating procedures for the EAN [12] regarding guideline development.

Methods

The Guideline was proposed at a meeting of the EAN Scientific Panel on Dementia and Cognitive Disorders in 2016. From this group a Task Force was convened, based on previous clinical experience in dementia management and research and geographical representation of the EAN member states. The EAN epilepsy panel was invited to appoint a representative (L.M.R.; following the decision to include treatment of epilepsy in dementia in the Guideline). Furthermore, related organizations were invited to appoint representatives for the task force: the European Alzheimer Disease Consortium [dementia experts within geriatrics (B.W.) and old age psychiatry (L.F.)], the European Geriatric Medicine Society (P.P.) and the European Association of Geriatric Psychiatry (M.V.). The patient organization, Alzheimer Europe, was invited to appoint a representative (J.G.).

Within the scope of medical management issues, the Task Force decided to address and prioritize those issues which were deemed most pressing. This included issues where there were significant variations in treatment across centers, regions and countries, unmet needs in relation to the management issues, additional costs associated with mismanagement, and

where mismanagement was associated with negative health consequences. The process by which the issues were selected were as follows: first a brain-storming session was carried out at a meeting of the entire EAN Scientific panel on Dementia and Cognitive Disorders. The brain-storming session resulted in the production of a list of possible issues to be addressed in the Guideline. This was followed by initial scoping searches, and further discussion and consensus-seeking via e-mail correspondence between members of the Task Force. Full consensus was reached for all recommendations. A list of five issues was agreed upon: systematic medical follow-up in dementia; management of vascular risk factors in dementia; management of pain in dementia; treatment of agitation/aggressive behavior with antipsychotics in dementia; and management of epilepsy in dementia. The Guideline was developed according to the Standard Operating Procedures of the EAN as described in the paper by Leone *et al.* [12], which included the development of an *a priori* protocol approved by the EAN (Appendix S1), and use of the GRADE framework [11] for development of guidelines, followed by final approval of the Guideline by the EAN Scientific Committee (Date of approval 14 April 2020). All co-authors were familiar with the GRADE framework. Please refer to other papers for details of the GRADE framework (e.g. Guyatt *et al.* [13]). The Task Force met at two in-person meetings. At the first meeting and according to the GRADE methodology a number of PICO (Population, Intervention, Comparator, Outcome) questions were formulated. At the final face-to-face meeting where all but two of the co-authors were present, the level of the quality of the body of the evidence (high, moderate, low, very low), the direction of the recommendation (for or against) and the strength of recommendation ('weak' or 'strong') were decided by consensus. This process also applied to those research questions where a Good Practice statement was made. The two co-authors not present were consulted following the meeting via email on whether they were in agreement with the decisions reached at the meeting. In instances where there was no evidence, the Task Force gave a Good Practice statement. 'Weak' and 'strong' have specific meanings which relate to the interpretation of a given recommendation within GRADE. Work on the Guideline was divided amongst all authors, so that two persons were responsible for the work on each topic, with K.F. and G.W. coordinating the work. Remaining members of the Task Force were regularly updated and involved in all aspects of the work throughout the process by the Task Force chairperson via email, and input was requested when necessary.

Search strategy, selection of studies, data extraction, risk-of-bias assessment and data synthesis

Six databases (including MEDLINE and Embase) were searched using relevant search terms including terms from controlled vocabularies and thesauruses. A single search string was developed for each management issue (See Appendix S1 for full search strategy). Each search strategy was reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist [14]. Eligible studies were randomized controlled trials (RCTs) which reported on relevant interventions and outcomes. For pain and vascular risk factors, observational studies were also included, since it was the opinion of the Task Force that, for these two issues, observational studies might contribute important evidence. Two of the co-authors (follow-up: D.R., K.F.; epilepsy: C.N., K.F.; vascular: A.V., K.F.; pain: M.K., K.F.; antipsychotics: E.S., K.F.) independently screened the identified references using an online software tool and piloted questionnaires first on title and abstract and secondly on full-text level. Data extraction was carried out by one author (K.F.) in a piloted Excel spreadsheet, and subsequently checked by the second co-author as with the screening. Financial disclosure statements and conflict of interest statements were extracted for all included studies and are reported in Table S1. Risk of bias for RCTs was assessed using the Cochrane's risk-of-bias assessment tool, version 1 [15] and, for observational studies, the Newcastle–Ottawa Quality Assessment Scale [16] was used. Data synthesis could be either as meta-analysis or narrative synthesis depending on the number of studies identified and which type of synthesis heterogeneity across studies permitted (See Appendix S1 for further details on the methods). Due to space restraints, results will largely be presented in supplementary tables and figures referred to throughout the text.

Section 1: Systematic medical follow-up in dementia

Background for systematic medical follow-up in dementia

Many patients with dementia are not followed by a medical doctor after initial diagnosis or may only be followed regularly for less than a year. Although no disease-modifying treatment is available for any of the neurodegenerative dementias, adequate management of associated medical conditions may reduce the burden of disease and functional decline [17–19]. In patients with dementia, some guidelines recommend

that patients should be followed by a specialist (e.g. neurologist or psychiatrist or geriatrician) [20]. However, many patients with dementia may never see a specialist [21]. Lack of insight and autonomy, an early and prominent symptom in many patients with dementia [22], may diminish the ability to make decisions about treatment [23] and is also associated with caregiver burden [24]. Cognitive and non-cognitive symptoms of dementia may constitute some of the barriers which impair access to medical care for patients with dementia [25].

Research question 1.1

Should home-living (non-institutionalized) patients with dementia be offered systematic medical follow-up in a memory clinic setting?

PICO question

Population: Home living (non-institutionalized) patients with dementia.

Intervention: Planned structured follow-up in the form of consultations offered in a medical dementia specialist team.

Comparator: Usual care.

Outcome: 1. Institutionalization (Important); 2. Caregiver burden (Important); 3. Acute hospital admissions (Important); 4. Activities of daily living (ADL; Critical).

Summary of evidence

We identified 400 references (after deduplication) for screening. No studies were eligible for inclusion (Figure S1 and Table S3).

Level of evidence

Not applicable.

Good Practice statement

The authors conclude that patients with dementia should be offered regular, preplanned medical follow-up. The setting will depend on the organization of local health services and should as a minimum include general practitioners with easy access to dementia specialists.

Supplemental considerations for systematic medical follow-up in dementia

We believe that regular, prescheduled follow-up in patients with dementia is important in order to address psychosocial as well as medical issues during the course of the condition. For optimal medical follow-up, visits in a multiprofessional setting (e.g. a memory clinic), where possible, are important.

Interaction between healthcare providers and patients with dementia is challenging due to lack of insight and self-awareness and other cognitive and non-cognitive symptoms of dementia leading to impaired autonomy [22,23], and may thus be better handled in a multiprofessional setting. Furthermore, we believe that multiprofessional memory clinics may be better suited for the management of cognitive, neuropsychiatric and other specific symptoms related to dementia disorders. Management of complex comorbidities, providing access for patients to participate in research and for meeting the needs of the caregiver are other important reasons. However, regular and preplanned medical follow-up may also be carried out in other settings, depending on the local organization of healthcare, for example, at the general practitioner's office. Easy access to a dementia specialist, such as a neurologist, psychiatrist or geriatrician, is desirable. Certain patients (e.g. patients with frontotemporal dementia, patients with Lewy-body dementia, patients with diagnostic uncertainty, patients with severe psychiatric and behavioral symptoms, and patients with familial disorders) should be given high priority for follow-up in a specialist setting, for example, a memory clinic setting.

Section 2: Management of vascular risk factors in dementia

Background for management of vascular risk factors in dementia

Vascular risk factors are associated with an increased risk of cognitive decline and dementia [26] and with the rate of progression of dementia and the occurrence of brain pathology such as small vessel disease [27,28], lacunar infarcts [29,30] and microbleeds [31]. Hence, optimal management of vascular risk factors may potentially modify the disease course in dementia. On the other hand, pharmacological treatment of vascular risk factors is associated with unwanted side effects such as an increased risk of intracerebral hemorrhage with anticoagulants [32] and dizziness and falls with anti-hypertensives. However, differentiating treatment based on cognitive status and the aforementioned side effects may not be warranted. It is likely that in many patients with dementia, vascular conditions and risk factors are identified at the time of the dementia diagnosis. Usually medical doctors would treat such conditions. However, the medical doctor may be in doubt as to whether there is any additional benefit for the prognosis of the dementia condition, or additional harm in patients with dementia, associated with treatment of the vascular condition. For

example, treatment with anticoagulation may be withheld in patients with dementia in instances where treatment would be initiated in non-demented patients due to potentially differential risk–benefit profiles. A number of medical societies have addressed the issue of anticoagulation in patients with dementia, either implicitly or explicitly. The American Academy of Neurology guidelines for stroke prevention in atrial fibrillation conclude that data in patients with atrial fibrillation who have ‘advanced’ dementia or frequent falls are insufficient to determine whether anticoagulants are safe and effective [33]. European Stroke Organization guidelines do not address the use of anticoagulants in dementia patients, but do not recommend them in patients with comorbid conditions (e.g. falls, uncontrolled epilepsy, gastrointestinal bleeding or poor compliance) [34]. The European Society of Cardiology guidelines state that anticoagulation should only be withheld ‘in selected patients with dementia where compliance and adherence cannot be ensured by a caregiver’ [35].

Research question 2.1

Should patients with atrial fibrillation (without previous stroke, but where there is indication for anticoagulants), and dementia be treated with anticoagulants?

PICO question

Population: Patients with dementia and atrial fibrillation and indication for treatment with anticoagulants and no previous stroke or transitory ischemic attack.

Intervention: Treatment with new oral anticoagulants or warfarin.

Comparator: No treatment with new oral anticoagulants or warfarin.

Outcome: 1. Major hemorrhagic events (Critical); 2. Global cognitive function (Important); 3. Mortality (Important); 4. Ischemic cerebrovascular event (Critical).

Summary of evidence

We identified 7135 (after deduplication) references (See Figure S2 and Table S3). We found one study that was eligible for inclusion [36]. In a retrospective cohort study in patients with dementia and atrial fibrillation (but no previous stroke), results from 3724 patients followed for a median (interquartile range) of 669 (805) days, were reported. Patients were either not treated (for unknown reasons) or treated with warfarin. Treatment was not associated with an increased risk of major hemorrhagic events [hazard ratio 1.07, 95% confidence interval (CI) 0.82–1.39], a

decreased risk of mortality (hazard ratio 0.88, 95% CI 0.77–1.01) and ischemic stroke (hazard ratio 0.74, 95% CI 0.54–1.03). The study did not report on global cognitive function (Tables S4 and S5). A financial disclosure statement and a conflict of interest statement were reported for the study (Table S1).

Level of evidence

The level of evidence was graded as very low (Tables S5 and S6).

Recommendation

The authors conclude that there should be a weak recommendation for treatment with anticoagulants in patients with dementia (without previous stroke) and atrial fibrillation.

Justification for recommendations

It is the opinion of the authors that the recommendation may be extended to include non-vitamin K oral anticoagulants, as these offer a better protection against ischemic stroke and a comparable safety profile [37]. There is a trend in the directions of the point estimates towards a beneficial profile, which importantly is in line with many other studies clearly demonstrating a beneficial effect of anticoagulation in patients with atrial fibrillation but no dementia [38]. In the opinion of the authors there is no reason to believe that some patients with dementia would not have a similar benefit from anticoagulation. Atrial fibrillation remains the commonest cause of ischemic stroke in the older population [39], and a study showed that elderly persons would accept a higher risk of a hemorrhagic event for a smaller reduction in the risk of an ischemic stroke [40]. There is no reason to believe that patients with dementia differ in this regard.

Research question 2.2

Does systematic management of vascular risk factors in patients with dementia slow the progression of dementia?

PICO question

Population: Patients with dementia and hypertension, hypercholesterolemia and type 2 diabetes mellitus.

Intervention: Systematic management of vascular risk factors (concomitant hypertension, hypercholesterolemia, type 2 diabetes mellitus).

Comparator: Usual care.

Outcome: 1. Institutionalization (Important), 2. Global cognitive function (Critical), 3. Mortality (Important), 4. ADL (Important).

Summary of evidence

One single-center retrospective cohort study was identified which reported on dementia patients with all three vascular risk factors [41] (Figure S2 and Tables S3 and S7). Twenty patients were followed for a mean (SD) of 30 (6) months. Treatment of one or more vascular risk factors was associated with less decline on Mini Mental State Examination [mean difference 2 (95 % CI -3.1 to 7.2)] compared to no treatment at all (Table S8). The study did not report data on the three remaining outcomes. No grading of evidence, using the GRADE framework, was carried out since it was the opinion of the authors that the evidence was insufficient to make a recommendation. Financial disclosures and a statement on conflict of interest were reported for the study (Table S1).

Level of evidence

Not applicable.

Good Practice statement

The authors conclude that systematic management of vascular risk factors should be performed in patients with mild to moderate dementia since prevention of cerebrovascular pathology may impact on the progression of dementia.

Justification for statement

We believe that systematic management of vascular risk factors is as important in patients with mild to moderate dementia as in patients without dementia as these factors are associated with adverse health outcomes and because an effect is unlikely to differ between patients with and without dementia [26–31]. It is the opinion of the authors that the value and attitudes of patients with dementia would not go against treatment, at least for a majority of patients. Since treatment may be associated with side effects, we believe that the recommendations should not extend to patients with severe dementia as the risk–benefit ratio becomes less clear, and because a short life expectancy may exclude any benefit from treatment.

Supplemental considerations for management of vascular risk factors in dementia

In patients with dementia, vascular risk factors may be neglected, and undertreated [42]. We believe that there is no reason to assume that patients with dementia benefit less from management of vascular risk factors than other patient groups. Furthermore, prevention of vascular pathology may provide an important added value in patients with vascular risk factors and dementia [43]. We believe that treatment should be individualized, issues of compliance should be considered, and

measures to ensure compliance and safety should be instituted where necessary. Review of existing medication should be carried out for drugs which may increase the risk of vascular pathology. Whether or not to institute pharmacological treatment should, in the opinion of the authors, be carefully considered in patients with falls, low compliance and advanced dementia and when life expectancy may be short because of safety concerns and because there may be uncertainty regarding the balance between harm and benefit.

Section 3: Management of pain in dementia**Background for management of pain in dementia**

Painful conditions, such as arthritis are as frequent in patients with dementia as in patients without dementia [44]. Moreover, patients with advanced dementia may not be able to report pain adequately because of impairment of memory or language, and pain may be difficult to assess [45]. Further, pain has been found to be associated with behavioral symptoms in patients with dementia [46]. Therefore, identification and treatment of pain is important but poses several challenges, which may both lead to overtreatment and undertreatment. For example, pain associated with malignancies and treatment of pain in an end-of-life situation may warrant use of opioids. However, use of opioids for the treatment of agitation when it is suspected to be attributable to pain may lead to overuse, which can be detrimental and constitutes a potential safety issue [47]. Conversely, use of milder analgesics more routinely in the presence of behavioral changes may be a rational intervention [48].

Research question 3.1

In patients with dementia, should opioids be discontinued?

PICO question

Population: Patients with dementia who are treated with opioids.

Intervention: Discontinuation of opioid treatment.

Comparator: Continuation of opioid treatment.

Outcome: 1. Psychotropic treatment (Important); 2. Global cognitive function (Critical); 3. Mortality (Important); 4. Pain (Critical); 5. Neuropsychiatric symptoms (Important).

Summary of evidence

We identified 1834 references (after deduplication) for screening. No references were eligible for inclusion (Figure S3 and Table S9).

Level of evidence

Not applicable.

Good Practice statement

The authors conclude that discontinuation of opioids should be considered in patients for whom there are no complaints of pain and no clear indication, where mild analgesics have not been tried and in patients in whom there is suspicion of side effects, such as rapid cognitive decline, sedation, falls, respiratory problems, constipation, nausea or reduced appetite.

Research question 3.2

Should behavioral symptoms in patients with dementia be treated with mild analgesics?

PICO question

Population: Patients with dementia and behavioral symptoms.

Intervention: Treatment with mild analgesics (paracetamol).

Comparator: No treatment with analgesics.

Outcome: 1. Psychotropic treatment (Important); 2. Global cognitive function (Important); 3. Agitation/aggression (Critical); 4. Neuropsychiatric symptoms (Important).

Summary of evidence

After screening, we included a single RCT [49] (Figure S3 and Table S9). In a placebo-controlled crossover study, 25 patients were randomized to either paracetamol or placebo. There was no difference in change in agitation over 8 weeks (as measured by the Cohen-Mansfield Agitation inventory). Use of paracetamol was found to be associated with less use of as-needed antipsychotics [mean difference -0.28 (95% CI -1 to 0.45); Tables S10 and S11]. The study did not report on neuropsychiatric symptoms or global cognitive function. Financial disclosure statement and statement on conflict of interest was reported for the study (Table S1).

Level of evidence

The level of evidence was graded as very low (Tables S11 and S12).

Recommendation

The authors conclude that there should be a weak recommendation against treatment of behavioral symptoms in persons with dementia with mild analgesics.

Justification for recommendations

The study identified for the present PICO did not demonstrate an effect of treatment with paracetamol

on behavioral symptoms in patients with dementia. Behavioral symptoms may be caused by many underlying causes, of which pain is one, and the rationale for the use of analgesics against behavioral symptoms would be to alleviate pain. Therefore, routine use of analgesics as a treatment for behavioral symptoms would neglect the identification of the true underlying cause and instead assume that in most cases pain is the causative factor. Moreover, the recommendation extends to all mild analgesics, as there is no reason to suspect efficacy will differ.

Supplemental considerations for management of pain in dementia

Assessment of pain in patients with dementia is important, but complicated by impaired communication, particularly in patients with advanced dementia [45]. We believe that behavioral signs must be included in the assessment of pain in patients who are impaired in verbal communication. Conversely, pain should also always be considered as a possible cause of behavioral signs. Conditions other than pain which may cause altered behavior must be ruled out before starting analgesics, and, if relevant, non-pharmacological treatment instituted. In patients receiving analgesics, always review treatment at regular intervals. We believe that when initiating treatment with analgesics, a stepwise approach starting with mild analgesics should be used. For safety reasons, long-acting opioids should not be introduced before short-acting opioids. Follow-up is important after initiation of analgesics (particularly opioids) to assess sedation, nausea and cognitive deterioration and after discontinuation to assess re-emergence of pain.

Section 4: Treatment of agitation/aggressive behavior with antipsychotics in dementia

Background for treatment of agitation/aggressive behavior with antipsychotics in dementia

Aggression or agitation may occur during the course of the condition without obvious reasons or when patients with dementia experience stress (e.g. changes in the environment during hospitalization), as a result of a physical condition, or as side effects of drug treatment. A number of meta-analyses have found that the efficacy of antipsychotics for treating agitation/aggression in patients with dementia, is modest and confers increased mortality and risk of cerebrovascular accidents [50–52]. In 2007 European regulatory agencies and the US Food and Drug Administration (FDA) issued warnings regarding the use of atypical antipsychotics in patients with

dementia. This was extended by the European Medicines Agency in 2008 and the FDA in 2009 to include a warning regarding the use of all antipsychotics, partly based on a number of large observational studies and meta-analyses that showed an increased mortality associated with treatment [53–59], which has been confirmed in subsequent studies [2,60].

However, antipsychotics may be used as first-line pharmacological treatment in agitation/aggression under certain preconditions (after all non-pharmacological measures have been proven to be without benefit or in the case of severe self-harm or harm to others) [61]. This includes the use of risperidone, haloperidol and aripiprazole. Antipsychotics confer modest benefits for short-term treatment of aggression/agitation in dementia [50–52], but these benefits have to be balanced against the risk of serious adverse events including increased mortality. The benefits are less clear-cut with long-term prescribing, but the mortality risk remains significantly elevated [53–59]. Therefore, minimizing and individualizing (with regular assessment of the individual risk–benefit ratio) the use of antipsychotics and ensuring that treatment with antipsychotics is only instituted when non-pharmacological treatment proves to be ineffective and when treatable causes of agitation/aggression have been ruled out, is necessary and will improve quality of life and function. A prescription or dose optimization of cholinesterase inhibitors or memantine should be carried out in parallel to other measures, since the effects of this may only be evident with a delay of 8 to 12 weeks. Because of the risk of severe hypersensitivity to antipsychotics in patients with Lewy-body dementia and Parkinson's disease dementia, the recommendations for Research questions 4.1 and 4.2 do not extend to these patients.

Research question 4.1

Should patients with dementia and agitation/aggressive behavior be treated with modern (atypical) antipsychotics compared to no pharmacological treatment?

PICO question

Population: Patients with dementia and agitation/aggressive behavior.

Intervention: Treatment with aripiprazole, zotepine, olanzapine, quetiapine, risperidone or clozapine.

Comparator: No pharmacological treatment.

Outcome: 1. Mortality (Important); 2. Agitation/Aggression (Critical); 3. Global cognitive function (Important); 4. Serious adverse events (Critical); 5. Caregiver burden (Important).

Summary of evidence

A total of 4058 references were screened and seven references were included [62–68] (Figure S4 and Table S13 and S14). Two references reported on different outcomes from the same study [65,66]. All studies included were RCTs. Studies were on risperidone (0.25 to 2 mg), quetiapine (25 to 200 mg) or olanzapine (2.5 to 15 mg). Meta-analysis was not performed due to heterogeneity in populations, length of interventions and outcome measures. There were no differences in mortality between interventions and across studies [62,64,65,67,68] (relative risk point estimates 0.85–2.08; not significant) or serious adverse events [62,63,66,67] (relative risk point estimates 0.89–1.9; not significant in all but one study [68]). However, there were, in general, very few events for the two outcomes, possibly because of the relatively low number of patients and short length of included trials (6–36 weeks; four studies \leq 12 weeks). For both global cognitive function and agitation/aggression scores, there was no difference in change score between treatment and placebo, except for a single study [67]. None of the studies reported on caregiver burden (Table S15). All studies reported financial statements. All but one study [67] reported receiving some or all of the funding for the study from pharmaceutical companies. One study did not include a statement on conflict of interest [62] (Table S1).

Level of evidence

The level of evidence was graded as low (Tables S15 and S16).

Recommendation

The authors conclude that there should be a weak recommendation against treatment of patients with dementia and agitation/aggressive behavior with modern (atypical) antipsychotics compared to no pharmacological treatment.

Justification for recommendations

It is the opinion of the authors that treatment of agitation and aggression (in the absence of severe self-harm or harm to others) should principally be directed at underlying causes, which in many instances are identifiable and to some extent treatable or manageable. Further, the effect of antipsychotics will (in the absence of psychotic symptoms) in many instances rely on a sedating effect, which in general is unwanted. Finally, use of antipsychotics in elderly and patients with dementia is associated with an increased risk of severe morbidity and mortality [2,53–60]. We believe that in light of this, and the fact that the included studies did not demonstrate an effect

of treatment, a majority of patients will prefer no pharmacological treatment.

Research question 4.2

Should patients with dementia and agitation/aggressive behavior be treated with modern (atypical) antipsychotics compared to haloperidol?

PICO question

Population: Patients with dementia and agitation/aggressive behavior.

Intervention: Treatment with aripiprazole, zotepine, olanzapine, quetiapine, risperidone or clozapine.

Comparator: Haloperidol.

Outcome: 1. Mortality (Important); 2. Agitation/Aggression (Critical); 3. Global cognitive function (Important); 4. Serious adverse events (Critical); 5. Caregiver burden (Important).

Summary of evidence

Four references reporting on the effect of atypical antipsychotics versus haloperidol were identified (Figure S4 and Tables S13 and S17). Three studies were RCTs [69–71] and one was an RCT with a crossover design [72]. Three studies compared risperidone (0.25 to 2 mg) to haloperidol (0.25 to 3 mg), and one study compared it with olanzapine (2.5 to 7.5 mg). There were no events in the studies reporting on mortality [69,70,72] or serious adverse events [71,72]. With regard to agitation/aggression, two studies on risperidone reported that treatment with atypical antipsychotics improved scores [71,72], and two studies, one on risperidone, the other on olanzapine, reported the converse [69,70]. However, none of the studies reported measures of variance (Tables S18 and S19). None of the studies reported on caregiver burden. One study did not include a financial statement [69], and two studies reported receiving funding for the study from pharmaceutical companies [71,72]. None of the studies included a conflicts of interest statement.

Level of evidence

The level of evidence was graded as *very low* (Tables S18 and S19).

Recommendation

The authors conclude that there should be a weak recommendation for treatment of patients with dementia and agitation/aggressive behavior with modern (atypical) antipsychotics compared to haloperidol when pharmacological treatment of agitation/aggressive behavior is necessary. Among modern (atypical)

antipsychotics, risperidone may be considered as first-line treatment when pharmacological treatment of agitation/aggressive behavior is necessary.

Justification for recommendations

Atypical antipsychotics is superior compared to placebo in reducing behavioral symptoms in patients with dementia, whereas haloperidol is not [73] and in elderly patients with various conditions, risperidone has been found to be as efficacious as haloperidol [74]. Moreover, several very large observational studies have demonstrated that haloperidol is associated with higher mortality, risk of pneumonia and cardiovascular disease compared to atypical antipsychotics (including risperidone) [53,54].

Research question 4.3

Should treatment with antipsychotics routinely be discontinued?

PICO question

Population: Patients dementia who are currently being treated with antipsychotics.

Intervention: Discontinuation of antipsychotics.

Comparator: Continuation of treatment.

Outcome: 1. Mortality (Important); 2. Neuropsychiatric symptoms (Critical); 3. Global cognitive function (Important); 4. Serious adverse events (Critical); 5. Caregiver burden (Important).

Summary of evidence

Eight references [75–82] reporting on the effect of discontinuation of antipsychotics were identified (Figure S4 and Table S13 and S20) from a total of six studies. Three studies were single-center and three were multi-center RCTs. A number of references reported on the same two studies. In detail, Devanand *et al.* [7879] reported on the same study as was the case with Ballard *et al.* [8182]. In both instances, the studies reported on the same cohort, but outcomes relevant for the PICO were reported in two different studies (e.g. mortality in one study and neuropsychiatric symptoms in another). A recent Cochrane meta-analysis [83] on discontinuation of antipsychotics assessed three studies not included in the present Guideline. One study did not report on any of the outcomes for the PICO [84] and two did not test a relevant intervention [85,86] (i.e. did not test the intervention which was defined in the PICO; Table S13). One additional study which was evaluated as satisfying the inclusion criteria and none of the exclusion criteria for the present Guideline, was included in the present Guideline but had not been included in the

previously published Cochrane review [82]. Study duration ranged from 4 weeks to 12 months, with one study reporting 42-month follow-up [82]. For studies reporting on mortality, there was a low event rate. Point estimates for relative risk varied from 0.19 to 3.11, with most [75,77–80], but not all [82] showing no significant differences. One study reported on serious adverse events (relative risk 2.80, 95 % CI 0.98–7.98) [79]. With regard to neuropsychiatric symptoms, two studies reported improvement with discontinuation [80,81] and two reported improvement with continuation [75,79]. A single study reported on global cognitive function and found favorable results for discontinuation [mean difference in change from baseline between the two groups 8 (95 % CI 2.20–13.80)] [81]. None of the identified studies reported on caregiver burden (Table S21). Two studies did not include a financial disclosure statement [75,76]. Four studies reported on conflicts of interest [75,78,81,82] (Table S1).

Level of evidence

The level of evidence was very low.

Recommendation

The authors conclude that there should be a weak recommendation for discontinuation in patients currently treated with antipsychotics. Discontinuation of antipsychotics may be considered in patients for whom there is no obvious indication and in patients in whom there is suspicion of side effects, such as rapid cognitive decline, sedation, falls, or extrapyramidal symptoms.

Justification for recommendations

The identified studies did not show a significant positive or detrimental effect of discontinuation of antipsychotics. Observational studies have clearly demonstrated that treatment is associated with increased mortality in patients with dementia [53–59].

Supplemental considerations for treatment of agitation/aggression with antipsychotics in dementia

We believe that treatment with antipsychotics may be relevant in selected patients with agitation and/or aggression. With the recommendations in this guideline, we wish to indicate that in those patients where antipsychotics are indicated, atypical antipsychotics will often be the first-line treatment. Most medical specialties may get involved in the decision to start or stop antipsychotic treatment. A detailed neuropsychiatric assessment including medical and drug history must be performed before initiating antipsychotic treatment.

In particular factors such as infection, dehydration, pain, pulmonary or cardiac disease, environmental factors such as changes in living conditions, and other stressors should be identified and treated adequately by non-pharmacological approaches. We believe that a principle of watchful waiting should be adopted before initiating treatment with antipsychotics. Anti-dementia medication (cholinesterase inhibitors and memantine) should be instituted as indicated. Communication and interaction with professional and family caregivers should be optimized. It is the opinion of the authors that antipsychotic treatment may be necessary in patients with severe agitation and/or aggression causing harm to themselves or to other people. Shared decision-making must be emphasized, and the patient as well as a legal guardian in instances where one has been appointed must be informed about the individual risk–benefit ratio. In instances where treatment with antipsychotics is initiated, starting low with slow up-titration to the minimally effective dose or until unacceptable side effects occur is, in the opinion of the authors, paramount. Follow-up for all patients should be planned and a preplanned stop date should be considered since symptoms may remit spontaneously. Long-term treatment (more than 3 months) may be necessary in a minority of patients and must be monitored carefully (e.g. effects on symptoms, body weight, cognition, extrapyramidal symptoms, sedation and ECG).

Section 5: Management of epilepsy in dementia

Background for management of epilepsy in dementia

Patients with dementia are at an increased risk of developing epilepsy [87,88], but it remains undetermined whether epilepsy is a common complication [89]. This highlights the importance of correct diagnosis and detailed monitoring of treatment, including the use of EEG, and the need for more research. Further, complex partial seizures may be overlooked due to cognitive impairment, overlap in symptomatology (e.g. fluctuations in level of consciousness and attention in patients with Lewy-body dementia) [90] and lack of knowledge among caregivers. A first seizure after a patient has been diagnosed with dementia may be interpreted as structural epilepsy (if no other competing factors which may lower the threshold of a seizure are identified), requiring consideration of institution of treatment. Underdiagnosis and undertreatment of epilepsy may therefore be common in patients with dementia. The aim of treatment of epilepsy in patients with dementia is to reduce seizures, mitigate the consequences of seizures, such as falls, and improve quality of life, and

treatment should be tailored to meet the needs of the individual patient. Moreover, some evidence suggests that seizures may affect cognition negatively, although confounders such as concurrent treatment with AEDs, underlying pathology and a general use of retrospective study design in studies examining the relationship, have been obstacles in elucidating this relationship [90–92]. Data from patients with dementia are lacking on this issue, but clinical experience suggests that persons with both congenital and acquired cognitive deficits are more prone to cognitive and sedative adverse effects of psychoactive drugs, including AEDs. Furthermore, pharmacodynamic and pharmacokinetic aspects, drug interactions and adverse effects may warrant special attention, particularly in elderly patients [93].

There is now a relatively large number of AEDs available with different modes of action and adverse effects. Clinical experience and some data suggest that, in older people, newer AEDs, such as lamotrigine and levetiracetam, are less prone to lead to cognitive side effects than traditional AEDs, such as carbamazepine, phenytoin and valproate [94].

Research question 5.1

Should patients with dementia and one or more seizures after diagnosis be treated with either levetiracetam/lamotrigine or carbamazepine/phenytoin/valproate?

PICO question

Population: Patients with dementia and one or more seizures of undetermined origin after the diagnosis of dementia.

Intervention: Treatment with either levetiracetam or lamotrigine.

Comparator: Treatment with either carbamazepine, phenytoin, valproate.

Outcome: 1. Serious adverse events (Important); 2. Global cognitive function (Critical); 3. ADL (Important); 4. Number of seizures (Critical).

Summary of evidence

A total of 323 references were identified (after deduplication) and screened. No studies were eligible for inclusion (Figure S5 and Table S22).

Level of evidence

Not applicable.

Good Practice statement

Newer anticonvulsants (including levetiracetam and lamotrigine) should be considered as first-line treatment of epilepsy in patients with dementia due to

their lower potential for drug interactions, lower incidence of adverse effects and linear pharmacokinetics.

Justification for statement

The recommendations pertaining to treatment of epilepsy in patients with dementia are based on indirect evidence from other patient groups including older patients treated for epilepsy. Newer anticonvulsants (including but not limited to levetiracetam and lamotrigine) have been found to have as good or better seizure control in many conditions [95] and show superior tolerability compared to older anticonvulsants [96].

Supplemental considerations for treatment of epilepsy in dementia

We believe that patients with dementia should be given the same attention and care as people without dementia regarding the management of epilepsy. It is important to regularly inquire about potential seizure markers with patients and their caregivers. Potential harms and benefits have to be considered when introducing a new AED and rapid follow-up ensured. It is the opinion of the authors that the choice of AED in a patient with dementia should be individualized. Due consideration should be given to the individual patient's concomitant pharmacological treatment and comorbidities, adverse effect profile of AEDs, effects on bone health and osteoporosis [97], and the availability of different drug formulations, dosing schedules, and risk of non-compliance. Monotherapy is recommended, and AEDs are better tolerated when started at low dose with gradual up-titration to as low a dose as possible to achieve seizure freedom. The aim is to minimize dose-dependent side effects (e.g. worsening of cognitive impairment, impaired gait, sedation, tremor, dizziness, visual disturbances and mood), to which older people are sensitive, and which may be particularly troublesome in patients with dementia. If valproate is considered, it is important to be aware of the risk of valproate encephalopathy (lethargy, reduced attention, behavioral changes) [98].

Discussion

This Guideline summarizes the evidence for the management of important medical issues in patients with dementia and gives recommendations for clinicians. One of the striking findings of the Guideline is the relative paucity of evidence for the medical management of medical issues in dementia, a chronic disorder with serious impact on patients, caregivers and society. Access to specialists is often limited in this patient population, and clinicians are faced with these management issues on a regular basis. The lack of scientific evidence,

however, does not confer the possibility of not acting; therefore, we have also sought to give guidance when no evidence was available, based either on indirect evidence or clinical judgement amongst the members of the Task Force which represents experts within the field of dementia research and care. The Guideline is based on the GRADE framework. This approach has strengths and weaknesses, as has also been highlighted by others [99,100], which also need to be considered.

In conclusion more research on the medical management issues covered in the present Guideline and other issues of the management of dementia is needed. Stakeholders such as patient advocacy groups, funding bodies, politicians and clinicians should work together to secure such opportunities, including funding for research.

Acknowledgement

The EAN supported this work by a grant to cover three face-to-face meetings and for part-time funding for K.F.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Guideline protocol.

Fig S1. Flow chart for papers screened for systematic medical follow-up.

Fig S2. Flow chart for papers screened for management of vascular risk factors in dementia.

Fig S3. Flow chart for papers screened for management of pain in dementia.

Fig S4. Flow chart for papers screened for treatment with antipsychotics.

Fig S5. Flow chart for papers screened for treatment of epilepsy in dementia.

Table S1. Financial disclosure statements and conflicts of interest of included papers.

Table S2. Papers screened for systematic medical follow-up in dementia.

Table S3. Papers screened for management of vascular risk factors in dementia.

Table S4. Characteristics of included studies (anticoagulation and atrial fibrillation in patients with dementia).

Table S5. Quality assessment and summary of findings (anticoagulation and atrial fibrillation in patients with dementia).

Table S6. Newcastle–Ottawa risk-of-bias assessment scale for cohort studies (anticoagulation and atrial fibrillation in patients with dementia).

Table S7. Newcastle–Ottawa risk-of-bias assessment scale for cohort studies (vascular care for patients with dementia).

Table S8. Characteristics of included studies (vascular care for patients with dementia).

Table S9. Papers screened for management of pain in dementia.

Table S10. Characteristics of included studies (mild analgesics for behavioral symptoms).

Table S11. Quality assessment and summary of findings (mild analgesics for behavioral symptoms).

Table S12. Results of Cochrane's risk-of-bias assessment tool, version 1 (mild analgesics for behavioral symptoms).

Table S13. Papers screened for treatment with antipsychotics in dementia.

Table S14. Characteristics of included studies (atypical antipsychotics vs. no pharmacological treatment).

Table S15. Quality assessment and summary of findings (atypical antipsychotics vs. no pharmacological treatment).

Table S16. Results of Cochrane's risk-of-bias assessment tool, version 1 (atypical antipsychotics vs. no pharmacological treatment).

Table S17. Characteristics of included studies (atypical antipsychotics vs. haloperidol).

Table S18. Quality assessment and summary of findings (atypical antipsychotics vs. haloperidol).

Table S19. Results of Cochrane's risk-of-bias assessment tool, version 1 (atypical antipsychotics vs. haloperidol).

Table S20. Characteristics of included studies (discontinuation of antipsychotics).

Table S21. Quality assessment and summary of findings (discontinuation of antipsychotics).

Table S22. Papers screened for management of epilepsy in dementia.

References

- Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. *The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. Alzheimer's Disease International. World Alzheimer Report: London, 2015: 2015.
- Zhai Y, Yin S, Zhang D. Association between antipsychotic drugs and mortality in older persons with Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimer's Dis* 2016; **52**: 631–639.
- Kristensen RU, Nørgaard A, Jensen-Dahm C, Gasse C, Wimberley T, Waldemar G. Changes in the prevalence of polypharmacy in people with and without dementia from 2000 to 2014: a nationwide study. *J Alzheimer's Dis* 2019; **67**: 949–960.
- Kristensen RU, Nørgaard A, Jensen-Dahm C, Gasse C, Wimberley T, Waldemar G. Polypharmacy and potentially inappropriate medication in people with dementia: a nationwide study. *J Alzheimers Dis* 2018; **63**: 383–394.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimer's Dement* 2011; **7**: 263–269.
- Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* 2014; **13**: 614–629.
- Filippi M, Agosta F, Barkhof F, et al. EFNS task force: The use of neuroimaging in the diagnosis of dementia. *Eur J Neurol* 2012; **19**: 1487–1501.
- Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *Eur J Neurol* 2012; **19**: 1159–1179.
- Hort J, O'Brien JT, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* 2010; **17**: 1236–1248.
- Schmidt R, Hofer E, Bouwman FH, et al. EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. *Eur J Neurol* 2015; **22**: 889–898.
- Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64**: 383–394.
- Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. *Eur J Neurol* 2015; **22**: 1505–1510.
- Guyatt G, Oxman A, Kunz R, Vist G, Falck-Ytter Y, Schunemann H. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008; **336**: 995–998.
- McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016; **75**: 40–46.
- Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: 1–9.
- http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- Tavassoli N, Perrin A, Bérard E, Gillette S, Vellas B, Rolland Y. Factors associated with undertreatment of atrial fibrillation in geriatric outpatients with Alzheimer disease. *Am J Cardiovasc Drugs* 2013; **13**: 425–433.
- Rattinger GB, Dutcher SK, Chhabra PT, et al. The effect of dementia on medication use and adherence among medicare beneficiaries with chronic heart failure. *Am J Geriatr Pharmacother* 2011; **10**: 69–80.
- Brecher DB, West TL. Underrecognition and Undertreatment of Pain and Behavioral Symptoms in End-Stage Dementia. *Am J Hosp Palliat Med* 2016; **33**: 276–280.
- National Institute for Health and Care Excellence. Dementia - Assessment, management and support for people living with dementia and their carers (NICE guideline 97). 2018;(June 2018).
- Helmer C, Pérès K, Pariente A, et al. Primary and secondary care consultations in elderly demented individuals in France. *Dement Geriatr Cogn Disord* 2008; **26**: 407–415.
- Starkstein SE. Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex* 2014; **61**: 64–73.
- Karlawish J, Casarett D, James B, Xie S, Kim S. The ability of persons with Alzheimer disease (AD) to make a decision about taking an AD treatment. *Neurology* 2005; **64**: 1514–1519 6p.
- Perales J, Turró-Garriga O, Gascón-Bayarri J, Reñé-Ramírez R, Conde-Sala JL. The Longitudinal Association between a Discrepancy Measure of Anosognosia in Patients with Dementia, Caregiver Burden and Depression. *J Alzheimer's Dis* 2016; **53**: 1133–1143.
- Bunn F, Burn AM, Goodman C, et al. Comorbidity and dementia: A scoping review of the literature. *BMC Med* 2014; **12**: 1–15.
- van Eersel MEA, Joosten H, Gansevoort RT, Slaets JPJ, Izaks GJ. Treatable Vascular Risk and Cognitive Performance in Persons Aged 35 Years or Older: Longitudinal Study of Six Years. *J Prev Alzheimer's Dis* 2019; **6**: 42–49.
- Zhao Y, Ke Z, He W, Cai Z. Volume of white matter hyperintensities increases with blood pressure in patients with hypertension. *J Int Med Res* 2019; **47**: 3681–3689.
- Avasthi P, Marshall WF. Impact of Normal Aging versus Hypertension, Abnormal BMI and Diabetes on White Matter Hyperintensity Volume. *Int Soc Differ* 2012; **83**: 1–29.
- Palacio S, McClure LA, Benavente OR, Bazan C, Pergola P, Hart RG. Lacunar Strokes in Patients With

- Diabetes Mellitus: Risk Factors, Infarct Location, and Prognosis. *Stroke* 2014; **45**: 2689–2694.
30. Mast H, Thompson JL, Lee SH, Mohr JP, Sacco RL. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. *Stroke* 1995; **26**: 30–33.
 31. Elmståhl S, Ellström K, Siennicki-Lantz A, Abul-Kasim K. Association between cerebral microbleeds and hypertension in the Swedish general population “Good Aging in Skåne” study. *J Clin Hypertens* 2019; **21**: 1099–1107.
 32. Malik AH, Yandrapalli S, Aronow WS, Panza JA, Cooper HA. Meta-analysis of direct-acting oral anticoagulants compared with warfarin in patients >75 Years of Age. *Am J Cardiol* 2019; **123**: 2051–2057.
 33. Culebras A, Messe SR, Chaturvedi S, Kase CS, Gronseth G. Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014; **82**: 716–724.
 34. Ringleb PA, Bousser MG, Ford G, et al. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**: 457–507.
 35. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardio-Thorac Surg* 2016; **50**: e1–e88.
 36. Subic A, Cermakova P, Religa D, et al. Treatment of Atrial Fibrillation in Patients with Dementia: A Cohort Study from the Swedish Dementia Registry. *J Alzheimer's Dis* 2018; **61**: 1119–1128.
 37. He Q, Sze CY, Shum TY, et al. Comparing clinical outcomes of NOACs with warfarin on atrial fibrillation with Valvular heart diseases: A meta-analysis. *BMC Cardiovasc Disord* 2019; **19**: 1–13.
 38. Segal JB, McNamara RL, Miller MR, et al. Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs. *J Gen Intern Med* 2000; **15**: 56–67.
 39. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The Epidemiology of Atrial Fibrillation and Stroke. *Cardiol Clin* 2016; **34**: 255–268.
 40. MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**(2 Suppl.): e1S–e23S.
 41. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009; **73**: 674–680.
 42. Lopponen M, Raiha I, Isoaho R, Vahlberg T, Puolijoki H, Kivela S-L. Dementia associates with undermedication of cardiovascular diseases in the elderly: a population-based study. *Dement Geriatr Cogn Disord* 2006; **22**: 132–141.
 43. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and dementia - a comprehensive review. *Ther Adv Neurol Disord* 2009; **2**: 241–260.
 44. Proctor WRHJ. Pain and cognitive status among nursing home residents in Canada. *Pain Res Manag* 2001; **6**: 119–125.
 45. Husebo BS, Achterberg W, Flo E. Identifying and Managing Pain in People with Alzheimer's disease and other types of dementia: a systematic review. *CNS Drugs* 2016; **30**: 481–497.
 46. Sampson EL, White N, Lord K, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards. *Pain* 2015; **156**: 675–683.
 47. Jensen-Dahm C, Gasse C, Astrup A, Mortensen PB, Waldemar G. Frequent use of opioids in patients with dementia and nursing home residents: A study of the entire elderly population of Denmark. *Alzheimer's Dement* 2015; **11**: 691–699.
 48. Jensen-Dahm C, Palm H, Gasse C, Dahl JB, Waldemar G. Postoperative treatment of pain after hip fracture in elderly patients with dementia. *Dement Geriatr Cogn Disord* 2016; **41**: 181–191.
 49. Chibnall JT, Tait RC, Harman B, Luebbert RA. Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia. *J Am Geriatr Soc* 2005; **53**: 1921–1929.
 50. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA* 2011; **306**: 1359–1369.
 51. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc* 1990; **38**: 553–563.
 52. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci* 2006; **7**: 492–599.
 53. Nasrallah HA, White T, Nasrallah AT. Lower mortality in geriatric patients receiving risperidone and olanzapine versus haloperidol: preliminary analysis of retrospective data. *Am J Geriatr Psychiatry* 2004; **12**: 437–439.
 54. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* 2007; **176**: 627–632.
 55. Wang PS, Schneeweiss S, Avorn J, et al. Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications. *N Engl J Med* 2005; **353**: 2335–2341.
 56. Chaddock-Heyman L, Mackenzie MJ, Zuniga K, et al. Higher cardiorespiratory fitness levels are associated with greater hippocampal volume in breast cancer survivors. *Front Hum Neurosci* 2015; **9**: 465.
 57. Trifirò G, Verhamme KMC, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MCJM. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. *Pharmacoepidemiol Drug Saf* 2007; **16**: 538–544.
 58. Gill SS, Bronskill SE, Normand S-LT, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; **146**: 775–786.
 59. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: Population based retrospective cohort study. *Br Med J* 2005; **330**: 445–448.
 60. Rao A, Suliman A, Story G, Vuik S, Aylin P, Darzi A. Meta-analysis of population-based studies comparing risk of cerebrovascular accident associated with first- and second-generation antipsychotic prescribing in

- dementia. *Int J Methods Psychiatr Res* 2016; **25**: 289–298.
61. Rabins P, Blacker D, Rovner B, *et al.* American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164**: 5–56.
 62. Zhong K, Tariot P, Mintzer J, Minkwitz M, Devine N. Quetiapine to treat agitation in dementia: a randomized, double-blind. Placebo-Controlled Study. *Curr Alzheimer Res* 2007; **4**: 81–93.
 63. Kurlan R, Cummings J, Raman R, Thal L. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* 2007; **68**: 1356–1363.
 64. Street JS, Clark WS, Gannon KS, *et al.* Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry* 2000; **57**: 968–976.
 65. Sultzer DLD, Davis SSM, Tariot PNP, *et al.* Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry* 2008; **165**: 844–854.
 66. Schneider L, Tariot P, Dagerman K, *et al.* Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006; **355**: 1525–1538.
 67. Ballard C, Margallo-Lana M, Juszczak E, *et al.* Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: Randomised double blind placebo controlled trial. *Br Med J* 2005; **330**: 874–877.
 68. Brodaty H, Ames D, Snowdon J, *et al.* A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* 2003; **64**: 134–143.
 69. Verhey FRJ, Verkaaik M, Lousberg R. Olanzapine versus haloperidol in the treatment of agitation in elderly patients with dementia: Results of a randomized controlled double-blind trial. *Dement Geriatr Cogn Disord* 2005; **21**: 1–8.
 70. Chan WC, Lam LC, Choy CN, Leung VP, Li SW, Chiu HF. A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. *Int J Geriatr Psychiatry* 2001; **16**: 1156–1162.
 71. De Deyn PP, Rabheru K, Rasmussen A, *et al.* A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 1999; **53**: 946.
 72. Suh G-H, Son HG, Ju Y-S, *et al.* A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioral disturbances. *Am J Geriatr Psychiatry* 2004; **12**: 509–516.
 73. Kongpakwattana K, Sawangjit R, Tawankanjanachot I, Bell JS, Hilmer SN, Chaiyakunapruk N. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. *Br J Clin Pharmacol* 2018; **84**: 1445–1456.
 74. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects. *Palliat Support Care* 2015; **13**: 1079–1085.
 75. Ruths S, Straand J, Nygaard HA, Aarsland D. Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study—the Bergen District Nursing Home Study (BED-NURS). *Int J Geriatr Psychiatry* 2008; **23**: 889–895.
 76. van Reekum R, Clarke D, Conn D, *et al.* A randomized, placebo-controlled trial of the discontinuation of long-term antipsychotics in dementia. *Int psychogeriatrics* 2002; **14**: 197–210.
 77. Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment—controlled pilot study. *J Geriatr Psychiatry Neurol* 1997; **10**: 119–126.
 78. Devanand DP, Pelton GH, Cunqueiro K, Sackeim HA, Marder K. A 6-month, randomized, double-blind, placebo-controlled pilot discontinuation trial following response to haloperidol treatment of psychosis and agitation in Alzheimer's disease. *Int J Geriatr Psychiatry* 2011; **26**: 937–943.
 79. Devanand DPP, Mintzer J, Schultz SK, *et al.* Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med* 2012; **367**: 1497–1507.
 80. Ballard CG, Thomas A, Fossey J, *et al.* A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. *J Clin Psychiatry* 2004; **65**: 114–119.
 81. Ballard C, Lana MM, Theodoulou M, *et al.* A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (The DART-AD Trial). *PLoS Medicine* 2008; **5**: 0587–0599.
 82. Ballard C, Hanney ML, Theodoulou M, *et al.* The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol* 2009; **8**: 151–157.
 83. Van Leeuwen E, Petrovic M, van Driel ML, *et al.* Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia. *Cochrane Database Syst Rev* 2018. <https://doi.org/10.1002/14651858.CD007726.pub3>.
 84. Findlay D, Sharma J, McEwen J, Ballinger B, MacLennan W, McHarg A. Double-blind controlled withdrawal of thioridazine treatments in elderly female inpatients with senile dementia. *Int. J Geriatr Psychiatry* 1998; **4**: 115–120.
 85. Cohen-Mansfield J, Lipson S, Werner P, Billig N, Taylor L, Woosley R. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home. *Arch Intern Med* 1999; **159**: 1733–40.
 86. Bergh S, Selbæk G, Engedal K. Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. *BMJ* 2012; **344**: e1566.
 87. Scarmeas N, Honig LS, Choi H, *et al.* Seizures in Alzheimer Disease. *Arch Neurol* 2009; **66**: 992–997.
 88. Cheng C-H, Liu C-J, Ou S-M, *et al.* Incidence and risk of seizures in Alzheimer's disease: A nationwide population-based cohort study. *Epilepsy Res* 2015; **115**: 63–66.
 89. Subota A, Pham T, Jetté N, Sauro K, Lorenzetti D, Holroyd-Leduc J. The association between dementia

- and epilepsy: A systematic review and meta-analysis. *Epilepsia* 2017; **58**: 962–972.
90. Beagle AJ, Darwish SM, Ranasinghe KG, La AL, Karageorgiou E, Vossel KA. Relative incidence of seizures and myoclonus in Alzheimer's disease, dementia with lewy bodies, and frontotemporal dementia. *J Alzheimer's Dis* 2017; **60**: 211–223.
 91. Helmstaedter C, Witt JA. Clinical neuropsychology in epilepsy: Theoretical and practical issues. *Handb Clin Neurol* 2012; **107**: 437–459.
 92. Vossel KA, Ranasinghe KG, Beagle AJ, et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann Neurol* 2016; **80**: 858–870.
 93. Vu LC, Piccenna L, Kwan P, O'Brien TJ. New-onset epilepsy in the elderly. *Br J Clin Pharmacol* 2018; **84**: 2208–2217.
 94. Kaur U, Chauhan I, Gambhir IS, Chakrabarti SS. Antiepileptic drug therapy in the elderly: a clinical pharmacological review. *Acta Neurol Belg* 2019; **119**: 163–173.
 95. de Campos MS, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses. *Int J Clin Pharm* 2018; **40**: 589–598.
 96. Zaccara G, Giovannelli F, Giorgi FS, Franco V, Gasparini S, Benedetto U. Tolerability of new antiepileptic drugs: a network meta-analysis. *Eur J Clin Pharmacol* 2017; **73**: 811–817.
 97. Fu J, Peng L, Li J, Tao T, Chen Y. Effects of second-generation antiepileptic drugs compared to first-generation antiepileptic drugs on bone metabolism in patients with epilepsy: a meta-analysis. *Horm Metab Res* 2019; **51**: 511–521.
 98. Beyenburg S, Back C, Diederich N, Lewis M, Reuber M. Is valproate encephalopathy under-recognised in older people? A case series. *Age Ageing* 2007; **36**: 344–346.
 99. Norris SL, Bero L. GRADE Methods for Guideline Development: Time to Evolve? *Ann Intern Med* 2016; **165**: 810.
 100. Rafiq M, Boccia S. Application of the GRADE Approach in the Development of Guidelines and Recommendations in Genomic Medicine. *Genomics Insights* 2018; **11**: 1–8.