Protocol for the European Academy of Neurology Guideline on

"Medical management issues in dementia"

Final version

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2. Introduction and objectives

An estimated 7.45 million people in Europe suffer from dementia, with the number expected to increase to 9.9 million in 2030. Dementia not only affects the patient with dementia and caregivers but also has important societal impact being a world-wide leading contributor to Disability Adjusted Life Years and in terms of related costs. Cost of dementia in Europe was estimated at 301.1 billion US$ in 2015 up from 238.6 billion US$ in 2010 (per cent increase 2010-2015: Central Europe: 5.7 %; Eastern Europe: 64.3 %; Western Europe: 25.0 %) [1], demonstrating the impact of dementia at present and as a major challenge for the future. Societies across Europe are challenged by the increased health care costs related to dementia and other health issues.

Many patients with dementia are elderly people with comorbidities, such as cardio-vascular conditions and diabetes, and patients with dementia disorders have an increased risk of developing epilepsy and agitation, aggression and psychosis. Furthermore, one of the consequences of cognitive impairment is inadequate reporting of physical and mental symptoms and of side effects related to drug treatment. Because the majority of patients with dementia in Europe are not offered systematic medical follow-up, treatable conditions may be overlooked or mismanaged, leading to accelerated functional decline, hospitalizations and increased mortality, and thus accelerated health care costs. This guideline will focus on the important role of the neurologist and other medical doctors in the general follow-up and medical management of patients with dementia.

Following, the objective of the guideline was to identify some of the most important management issues in dementia and to provide recommendations on how these should be addressed. The responsibility for the long-term management and care of patients with dementia is multidisciplinary and is often coordinated by community based dementia teams or specialist nurses. This guideline

will focus on issues related to dementia disorders in general, where the medical doctor can make a unique contribution to the treatment and care of patients with dementia.

3. Selection of the Guideline Task Force

The Guideline was proposed at a meeting of the EAN Scientific Panel on Dementia and cognitive disorders in 2016 after which members of the Panel were asked whether they were interested in participating in the Task Force. From the group of members interested in participation, a Task Force was convened, based on previous clinical experince in dementia and research, so that both junior and senior researchers and clinicians were represented. Furthermore, geographical representation of the EAN member states was sought with representatives from Western, Eastern, Northern and Southern Europe. The EAN epilepsy panel was invited to appoint a representative. Furthermore the following related organizations were invited to appoint scientific representatives for the task force: The European Alzheimer Disease Consortium (who appointed leading dementia experts within geriatrics and old age psychiatry), the European Union Geriatric Medicine Society and the European Association of Geriatric Psychiatry. Finally, the patient organization, Alzheimer Europe, was invited to appoint a representative.

4. Process and criteria for selecting management issues for the Guideline

The medical management issues for this guideline were selected based on the following criteria:

- Reason to assume that a reasonable amount of evidence was available, enabling an ability to formulate a recommendation
- Reason to assume significant variations in treatment across centres, regions, and countries
- Reason to assume that there were unmet needs in relation to the management issue
- Reason to assume that there are additional costs associated with mismanagement

- Reason to assume that mismanagement is associated with negative health consequences

At a brain-storming session in 2016 at a meeting of the EAN Scientific Panel on Dementia and cognitive disorders, a list of possible issues was developed and included the following:

- Effects of systematic medical follow-up in dementia
- Effects of systematic review of medication in patients with dementia
- Treatment of pain in dementia
- Treatment with anti-psychotics in dementia
- Management of vascular risk factors in dementia
- Management of epilepsy in dementia
- Sleep in dementia
- Prevention of falls in dementia
- Nutrition in dementia
- Statins and dementia
- Anesthesia and dementia
- Hip fracture in dementia
- End-of-life decisions in dementia
- Access to research
- Wandering and dementia
- Driving and dementia

After initial scoping searches to identify relevant literature, a shortened list was developed, and through further discussion and consensus seeking via e-mail correspondence, a final list of 5 issues was agreed upon, and consisted of the following:

4.1 Medical management issues

- *Management of epilepsy in dementia*

Patients with dementia are at an increased risk of developing epilepsy during the course of the disease [2]. Seizures, in particular complex partial seizures, may be overlooked due to the cognitive impairment of the patients, and lack of awareness among the caregivers. Untreated epilepsy may worsen cognitive performance and lead to accelerated functional decline. Correct medical management is crucial for seizure control, and should be tailored to the needs of the patient. This includes awareness of adverse effects of some anti-epiliptic drugs (AED) regarding worsening cognitive function and psychiatric symptoms.

- *Management of vascular risk factors in dementia*

Vascular risk factors are associated with an increased risk of dementia and rate of progression of dementia [3]. Hence, optimal management of vascular risk factors may modify the disease course in dementia, but may also be associated with additional harm.

- *Effects of systematic medical follow-up in dementia*

Dementia is a serious neurological disease, which is associated with an increased morbidity and mortality, as well as a lower quality of life for patients and carers [4]. Moreover, associated costs are amongst the highest across disease groups [1]. Nevertheless, many patients with dementia are not followed up by a doctor following initial diagnosis, or may only be followed regularly for less than 1 year. Although no disease-modifying treatment is available for any dementia diseases, many therapies may reduce the burden of disease and functional decline. This includes treatment of comorbidities, identifying vascular risk factors, and conditions associated with pain.

- *Treatment with anti-psychotics in dementia*

Within the last 10-15 years, antipsychotics have moved from first-line to second-line treatment with regards to behavioural disturbances in dementia. This change in management has been motivated by studies questioning efficacy, but equally important findings of serious adverse effects [5–7], which have prompted regulatory authorities to issue warnings. However, antipsychotics may be necessary in cases with psychotic symptoms with a potential of self-harm or harm to others, or severe aggression or agitation in patients with dementia [8]. Therefore, minimizing the use of antipsychotics and ensuring that treatment with antipsychotics is only instituted in those instances where the treatment is really needed, will likely improve quality of life and function.

- *Treatment of pain in dementia*

Conditions associated with pain, such as arthritis are as frequent in patients with dementia as in cognitively intact patients [9]. Patients with advanced dementia may not be able to report pain adequately due to impairment of memory problems or language. Thus, attempts have been made for developing methods for assessing pain in patients with dementia [10]. Available evidence indicates both possible undertreatment of pain [11] and a disproportionate high use of opioids in patients with dementia [12]. It is important not to overlook pain in a patient with dementia, and it is well-known that pain may be associated with behavioural symptoms in patients with advanced dementia [13]. On the other hand, excessive use of opioids is not justified and may be detrimental and constitutes a potential safety issue. The problem is compounded by the difficulty of assessing pain in patients with dementia [14].

5. Existing guidelines with relevance to the present EAN Guideline

A number of EAN and EFNS guidelines exist on different aspects in dementia such as diagnosis and treatment. This includes use of imaging in the diagnosis of dementia [15], the diagnosis and management of disorders related with dementia [16], diagnosis and management of Alzheimer´s disease [17], and concomitant use of choline-esterase inhibitors and memantine in Alzheimer´s disease [18]. None of the guidelines address the area of medical management in dementia, and thus are not overlapping with the present guideline. To identify additional existing relevant and thematically overlapping guidelines from other organisations and entities, a search in Pubmed

(Search terms ”epilepsy” AND ”dementia” AND ”guideline”; ”pain” AND ”dementia” AND ”guideline”; ”medical follow-up” AND ”dementia” AND ”guideline”; ”anti-psychotics” AND ”dementia” AND ”guideline”; ”vascular” AND ”dementia” AND ”guideline”; ”medical management” AND ”dementia” AND ”guideline”. Limits: Published in English 2006 and onwards) was carried out and the Task Force were queried regarding whether any of the members had knowledge of other guidelines missed in the search (see below and appendices A and B for result of the search and evidence call). In general, only guidelines addressing treatment of pain and treatment with anti-psychotics in patients with dementia were identified. No general guidelines on medical management issues in dementia were identified. Results of the search:

- Management of epilepsy in dementia: None identified
- Management of vascular risk factors in dementia: None identified
- Effects of systematic medical follow-up in dementia: None identified
- Treatment with anti-psychotics in dementia: See appendix A
- Treatment of pain in dementia: See appendix B

6. Medical management issues, research questions and PICO questions

6.1 Process of creating PICO questions

At a meeting in 2018, the Task Force convened to develop the PICO questions. Prior to the meeting, Task Force members were asked to suggest relevant PICO questions (within the 5 management issues already decided on), which were subsequently circulated amongst members in the time leading up to the meeting. Furthermore, a list of outcomes for each PICO, mostly patient-centred, and at least one which reflected possible adverse effects of the intervention, was produced. At the meeting the PICO questions were discussed and, by consensus, agreed upon. Lastly, the

importance of these outcomes was rated and classified as critical, important and not important according to the GRADE methodology [19].

6.2 Research questions and PICOs

6.2.1 Management of epilepsy in dementia ***(Appendix E)***

A first seizure of undetermined etiology after a patient has been diagnosed with dementia may be interpreted as structural epilepsy (if not other competing factors which may lower the threshold of a seizure is indetified), requiring institution of treatment. However, some AEDs may have adverse effects, which may be more pronounced or severe in patients with dementia or may not be as effective. Clinical experience suggests that newer AEDs, such as lamotrigine and levetiracetam, are less prone to give cognitive side effects than traditional AEDs, such as carbamazepine/phenytoin/valproate.

For the present research question and PICO question, we will include RCTs only since it was the opinion of the Task Force, that these types of studies were the only relevant to address these questions.

<u>Research question 1:</u> Should patients with dementia and 1 or more seizures after diagnosis be treated with either levetiracetam/lamotrigine or carbamazepine/phenytoin/valproate?

Population	Patients with dementia and 1 or more seizures of undertermined origin after the diagnosis of dementia
Intervention	Treatment with either levetiracetam or lamotrigin
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*

6.2.2 Management of vascular risk factors in dementia ***(Appendix F)***

It is likely that in many patients, vascular conditions and risk factors are identified for the first time in a patient who has developed dementia. Usually MDs would treat such conditions – as they would in patients without dementia. However, in these situations the MD may be in doubt 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. One such instance would be regarding a newly diagnosed atrial fibrillation in a patient with dementia without a stroke. Would anti-coagulation in such an instance lead to additional benefits (e.g. slower disease progression through prevention of strokes) or additional harm (e.g. through hemorrhages) ? Both observational and RCTs will be included in the analysis.

<u>Research question 1:</u> Should patients with dementia (without previous stroke) and atrial fibrillation be treated with anti-coagulants?

Population	Patients with dementia and atrial fibrillation and no previous stroke or TCI
Intervention	Treatment with NOACs or warfarin
Comparator	No treatment with NOACs or warfarin

Outcome	1. Major hemoragic events	*Critical*
	2. Global cognitive function	*Important*
	3. Mortality	*Important*
	4. Ischemic vascular event	*Critical*

Researh question 2. Does systematical management of vascular risk factors in patients with dementia slow the progression of dementia?

Population	Patients with dementia	
Intervention	Systematic management of vascular risk factors (Hypertension, hypercholesterolemia, diabetes mellitus type 2)	
Comparator	Usual care	
Outcome	1. Institutionalisation	*Important*
	2. Global cognitive function	*Critical*
	3. Mortality	*Critical*
	4. ADL	*Important*

6.2.3 Effects of systematic medical follow-up in dementia ***(Appendix G)***

We aim at assessing the effect of intensive pre-planned follow-up versus usual care (e.g. the option to contact a GP in case of questions or medical problems). In contrast to other comparable disorders such as Parkinson´s disease, where in some countries and regions, there is usually an offer of

routine follow-up through a specialist, patients with dementia are often not offered systematic follow-up.

For the present research question and PICO question, we will include RCTs only since it was the opinion of the Task Force, that these types of studies were the only relevant to address these questions.

Research question 1: Should home-living (non-institutionalised) patients with dementia be offered systematic medical follow-up in a memory clinic setting?

Population	Home-living (non-institutionalised) 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. Institutionalisation	*Important*
	2. Caregiver burden	*Important*
	3. Acute hospital admissions	*Important*
	4. ADL	*Critical*

6.2.4 Treatment with anti-psychotics in dementia ***(Appendix H)***

Treatment with antipsychotics may be relevant when patients with dementia develop severe agitation, aggression or psychosis with a potential for self-harm or harm to others. This may happen during the course of disease without reasons or when patients with dementia experience changes in the environment, e.g. during hospitalization, or as a result of a physical condition, or as side effects of drug treatment. It is well documented that antipsychotics confer modest benefits for short-term

treatment of aggression and psychosis in dementia, but these benefits have to be balanced against the risk of serious adverse events including increased mortality. The benefits are less clear-cut with longer term prescribing, but the mortality risk remains significantly elevated . General practitioners as well as hospitalbased and primary care specialists, including neurologists, may get involved in the decision to start or stop antipsychotic treatment. Whenever possible a (geriatric) psychiatrist should be involved in the initiation of antipsychotic treatment.

Before initiating treatment with an antipsychotic patients should be systematically assessed for physical conditions as a cause of agitation/aggression/psychosis, such as UTI, pain, respiratory or cardiac problems, etc., and be treated for this physical cause. If no apparent physical cause, a systematic assessment for potentially stressful environmental changes should be carried out and non-pharmacological approaches should be tested. Psychosocial approaches include general interventions e.g. validation, behavioral management, education of caregivers/nurses, and patient-centered interventions (e.g. cognitive stimulation, music therapy, sensory stimulation, reminicence treatment). If non-pharmacological approaches have no effect then an antipsychotic may be needed. This guideline will focus on patients with dementia who develop agitation, aggression, or psychosis during the course of their dementia disease, and not on patients with pre-existing psychiatric conditions. We include only RCTs, both on effects of treatment as well as on discontinuation of treatment, since these types of studies are prevalent, and will provide rich data to address this issue.

<u>Research question 1:</u> Should patients with dementia and agitation/aggressive behaviour be treated with atypical anti-psychotics compared to no pharmacological treatment?

Population	Patients with dementia and agitation/aggressive behavior

Intervention	Treatment with aripripazole, zoleptil, olanzapine, quetiapin, risperidone or clozapine	
Comparator	No pharmacological treatment	
Outcome	1. Mortality	*Critical*
	2. Agitation/Aggression	*Important*
	3. Global cognitive function.	*Important*
	4. Serious adverse events	*Critical*
	5. Caregiver burden	*Important*

<u>Research question 2:</u> Should patients with dementia and agitation/aggressive behaviour be treated with atypical anti-psychotics compared to haloperidol?

Population	Patients with dementia and agitation/aggressive behavior	
Intervention	Treatment with aripripazole, zoleptil, olanzapine, quetiapin, risperidone or clozapine	
Comparator	Haloperidol	
Outcome	1. Mortality	*Critical*
	2. Agitation/Aggression	*Important*
	3. Global cognitive function.	*Important*
	4. Serious adverse events	*Critical*
	5. Caregiver burden	*Important*

<u>Research question 3:</u> Should treatment with antipsychotics be routinely discontinued?

Population	Patients dementia who are currently being treated with anti-psychotics	
Intervention	Discontinuation of antipsychotics	
Comparator	Continuation of treatment	
Outcome	1. Mortality	*Critical*
	2. Neuropsychiatric symptoms	*Important*
	3. Global cognitive function.	*Important*
	4. Serious adverse events	*Critical*
	5. Caregiver burden	*Important*

6.2.5 Assessment and treatment of pain in dementia ***(Appendix I)***

Identification and treatment of pain in dementia poses several challenges, which may both lead to overtreatment and undertreatment. As with behavioral changes, pain is often a symptom of underlying disease, and not a disease in itself. Therefore, efforts to identify the cause of pain should also be done in patients with dementia. In many instances such as pain associated with malignancies or treatment in an end-of-life situation may warrant use of opioids. However, routine use of opioids for the treatment of agitation when it is suspected to be due to pain, may lead to overuse. Conversely, use of milder analgesics more routinely in the presence of behavioral changes may be a rational intervention.

For the present research questions, both observational studies and RCTs will be included.

<u>Research question 1:</u> In patients with dementia, should opioids be discontinued?

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	*Critical*
	4. Pain	*Important*
	5. Neuropsychiatric symptoms	*Important*

<u>Research question 2:</u> Should behavioral symptoms in patients with dementia be treated with mild analgesics?

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*

7. Methods of the systematic review, meta-analysis and development of the Guideline

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [19–33] will be used in the development of the present guideline as the preferred rating system for development of EAN Guidelines [34]. The methodology described in [34,35] will be followed. To

educate and familiarize the members of the Task Force with the GRADE process, the GRADE papers have been circulated, and webinars through the EAN webpage has been made available. Furthermore, a short lecture was held at the Kick-off meeting in 2018 by the chairperson, and a longer workshop will be conducted at the meeting in November 2018 (see appendix C). The purpose of the systematic review is to carry out a comprehensive search and review of published and unpublished evidence pertaining to the research questions and PICO questions (see above and below).

7.1 Information sources and search

The literature searching will be carried out according to the guidance prescribed by The Cochrane Handbook [36].

Searching bibliographic databases:

The following bibliographic databases will be searched to identify published studies:

- MEDLINE and MEDLINE in Process (Ovid Interface);
- Embase (Ovid Interface);
- PsycINFO (Ovid Interface);
- ALIOS (via www.medicine.ox.ac.uk/alois)*
- PubMed (NLM interface)** and
- The Cochrane Library: CENTRAL database (Wiley Interface).

* ALIOS is the specialized register of the Cochrane Demetria Group. It is has been off-line for a while for an upgrade. We will attempt to search this resource, if access is possible.

** search strategy limited to e-publications.

The bibliographic database search strategy will take the following form:

((search terms for dementia) AND (search terms for interventions or PICO topic) and (a study design search filter to identify studies reporting randomized controlled trials OR a study design search filter to identify studies reporting observational studies))

Sample search strategies for each PICO, formatted for the MEDLINE database (Ovid interface), are included in appendix D. The study design search filter to identify studies reporting randomized controlled trials will be the Cochrane Highly Sensitive Search Strategy (known as The Cochrane HSSS) [37] . The Scottish Intercollegiate Guidelines Network (SIGN) Observational study design search filter will be used to identify studies reporting observational study designs [38]. No other limits (e.g. date, publication or language) will be placed on the search.

Searching supplementary search methods:

Supplementary search methods will be used to identify unpublished studies or studies not indexed in the bibliographic databases identified above [39]. The following search methods are indicated:

Citation searching studies included at full-text for each PICO:

Studies will be forwards citation searched in Web of Science (Clarivate Analytic) and backwards searched by task-force members. All records identified will be exported to Endnote (X7.2) where a search will be made to identify studies reporting randomized trials or observational studies;

Author contact:

We will attempt to contact corresponding authors via e-mail for studies included as full-text for each PICO. The purpose of this contact will be to elicit any further and/or unpublished studies;

Call for evidence:

We will produce a call for evidence from within task force networks and, more broadly, the EAN and wider networks (where links exist). This call for evidence will take the form of a global e-mail asking respondents to identify any potentially relevant studies.

Resource limits prohibit the searching of trials registers, web-searching and handsearching of conferences.

Recording the process of literature searching:

The search strategies for each search will be reported to PRISMA reporting standards to ensure transparency and replicability [40,41]. Study data will be retained in RIS format for export into the screening tool for the reviews.

7.2 Study selection

The studies identified through the searches for each PICO will be screened by two members of the TF independently for inclusion. A software solution will be used to manage identified studies and to carry out the screening process. The screening process will be carried out in a two-step approach with an initial screening carried out on title and abstract level. In the second step full texts of the studies identified at this step will be retrieved for further screening. A consensus decision will be sought, and in case this is not possible, a third member of the TF will be asked to review the study with the aim of arbitrition. The third reviewer has the final say if no consensus can be reached.

A checklist has been developed for the screening:

- Population: Eligible ? (Yes/no)
- Intervention: Eligible ? (Yes/no)
- Study design: Observational/RCT (Eligibility will differ across PICOs)
- Included outcomes: (Eligibility will differ across PICOs)

7.3 Data collection process

Data from included studies will be extracted by two members of the TF independently in a piloted excel spreadsheet, and transferred to GRADEpro.

7.4 Data items

Data on the following items will be extracted from included studies:

Study design

Number of participants

Population characteristics (Age, gender, baseline MMSE, diagnosis)

Intervention

Comparator

Statistical methods

Outcome measures

7.5 Synthesis of results

We plan to carry out meta-analyses of extracted effect estimates if this is deemed relevant (e.g. due to inclusion of very few studies). Otherwise, a narrative synthesis of the data will be carried out.

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Appendix A: Existing guidelines (Treatment with anti-psychotics in dementia)

Ref	Year	Title	Published/ endorsed by	Description
[42]	2016	The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia	The American Psychiatric Association	Specific guideline on antipsychotic treatment in patients with dementia
[43]	2015	A consensus guideline for antipsychotic drug use for dementia in care homes. Bridging the gap between scientific evidence and clinical practice.		Specific guideline on antipsychotic treatment in patients with dementia
[44]	2014	Practice guideline for the treatment of patients with Alzheimer´s disease and other dementias	American Psychiatric Association	General guideline on treatment of patients with dementia including recommendations on

				treatment with antipsychotics. Update of the original Guideline from 2007
[45]	2006	Scottish Intercollegiate Guideline Network, 2006. Management of patients with dementia	Scottish Intercollegiate Guideline Network	General guideline on treatment of patients with dementia including recommendations on treatment with antipsychotics.
[46]	2006	NICE Guideline: Dementia: supporting people with dementia and their carers in health and dementia and their carers in health and social caresocial care	NICE	General guideline on treatment of patients with dementia including recommendations on treatment with antipsychotics.

Appendix B: Existing guidelines (Treatment of pain in dementia)

Ref	Year	Title	Published/endorsed by	Description
[47]		Number 8 - The assessment of pain in older people-National Guidelines	The Royal College of Physicians, the British Pain Society & The British Geriatrics Society	The Guideline focuses on older people, but has recommendation to deal with pain in patients with cognitive impairment
[48]		Pain in Residential Aged Care Facilities Management Strategies.	Australian Pain Society	The Guideline focuses on old persons in residential care. Addresses issues related to assessment and treatment of pain in patients with dementia and cognitive impairment

Appendix C: Time table

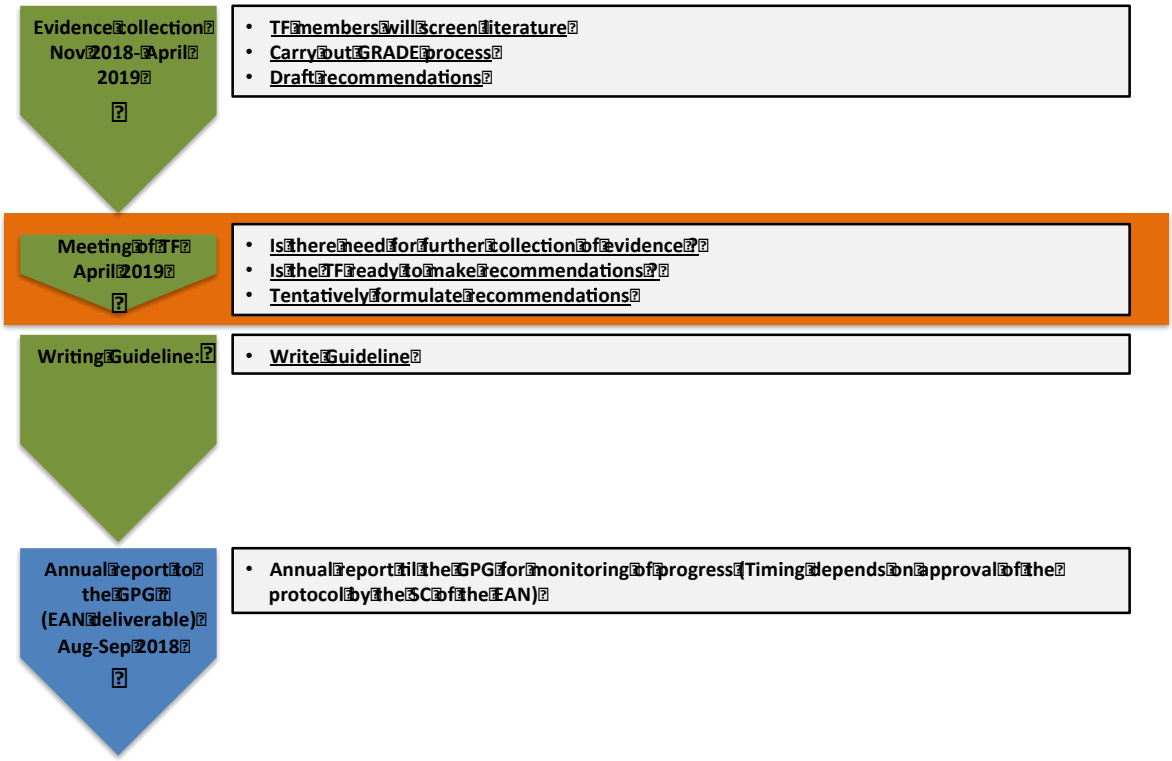
Flowchart: EAN guideline on medical management issues in dementia
(Updated 19th of June 2018 by Kristian Steen Frederiksen, chairperson)

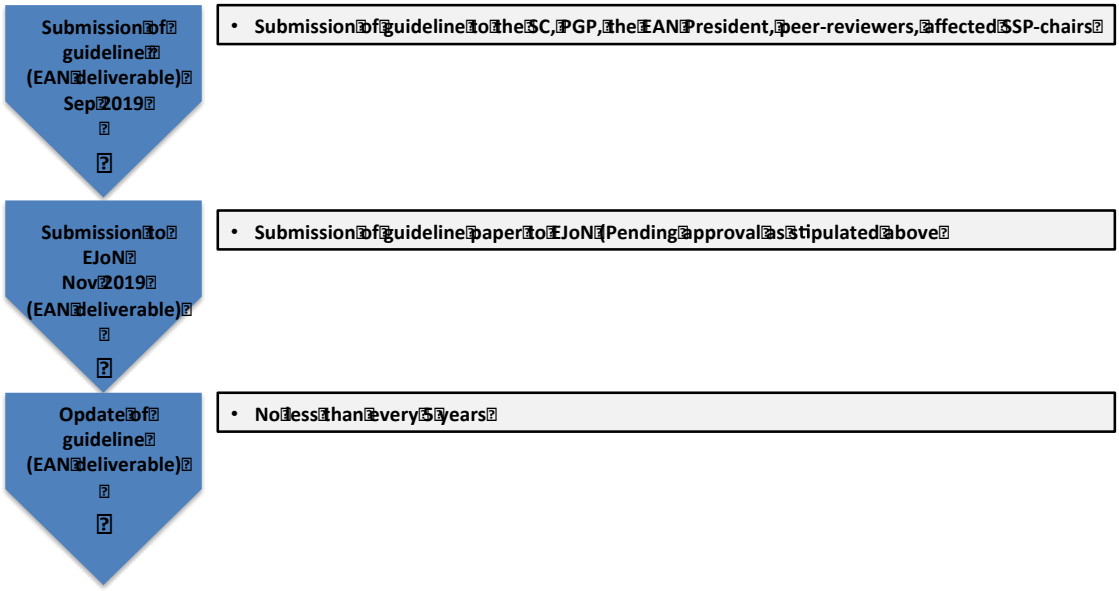
EAN Deliverables indicated by blue

Meetings of the Task Force highlighted in orange

TF=Task force
EAN=European Academy of Neurology
ROI=Register of interest
SC=Scientific committee
GPG=Guideline production group
EJoN=European Journal of Neurology
SSP=Subspeciality scientific panel


TF-Protocol for the production of the guideline March 2018-July 2018
The protocol should include: Title, objectives, names of TF members, rationale and need, existing guidelines which may be relevant, search strategy (including search strings), method for reaching consensus, clinical questions and outcomes (described in terms of PICO according to GRADE), time frame
Submission of TF-protocol (EAN deliverable) August 2018
The protocol will be submitted to the SC and the GPG for approval.
When approved the TF will have 18-24 months to complete the guideline
The GPG may assist the TF throughout the process with methodological issues.
Approval of protocol and endorsement of TF September-October 2018
Approval and endorsement by SC and EAN
Meeting of TF Nov 2018
Participants: TF (Topic leader, chairperson, search specialist)
Presentation of search results
Workshop on GRADE
Plan for GRADE and meta-analysis


Evidence collection Nov 2018- April 2019
TF members will screen literature
Carry out GRADE process
Draft recommendations
Meeting of TF April 2019
Is there need for further collection of evidence?
Is the TF ready to make recommendations?
Tentatively formulate recommendations
Writing Guideline:
Write Guideline
Annual report to the GPG (EAN deliverable) Aug-Sep 2018
Annual report til the GPG for monitoring of progress (Timing depends on approval of the protocol by the SC of the EAN)


Submission of guideline (EAN deliverable) Sep 2019
Submission of guideline to the SC, PGP, the EAN President, peer-reviewers, affected SSP-chairs
Submission to EJoN Nov 2019 (EAN deliverable)
Submission of guideline paper to EJoN (Pending approval as stipulated above
Opdate of guideline (EAN deliverable)
No less than every 5 years

Appendix D: Search strings

Epilepsy PICO

Research question 1: Should patients with dementia and 1 or more seizures after diagnosis be treated with either levetiracetam/lamotrigine or carbamazepine/phenytoin/valproate?

Database: MEDLINE
Host: Ovid
Data parameters: 1946 to present
Date searched: Thursday June 21st 2018
Search strategy:

#	Searches	Results
1	exp Dementia/	146709
2	(Dement$ or Alzheimer$ or Amnes$ or Parkinson$ or Huntington$ or lewy$ bod$ or pick$ disease or Posterior cortical atrophy or aphasia or (brain adj1 (disease$ or syndrome$)) or binswanger* or Progressive supranuclear palsy or Steele-Richardson-Olszewski syndrome or Frontotemporal disorder$ or Frontotemporal degeneration or Corticobasal degeneration or Corticobasal syndrome or cognitive disorder$ or Vascular cognitive).ti,ab,kw,ot.	316142
3	*Amnesia/	4649
4	exp Parkinsonian Disorders/	71220
5	*Huntington Disease/	8822
6	*Supranuclear Palsy, Progressive/	1685
7	1 or 2 or 3 or 4 or 5 or 6	348756
8	(Levetiracetam$ or Keppra or Elepsia or Matever or Spritam or Kopodex or Lo59 or lo 59 or N03AX14 or 102767-28-2).ti,ab,kw,ot.	3128
9	(Lamotrigin$ or Lamictal or Labileno or Lamepil or Lamictin or Lamodex or Lamogine or Lamotrix or Neurium or NO3AX09 or 84057-84-1).ti,ab,kw,ot.	4807
10	8 or 9	7219
11	randomized controlled trial.pt.	462372
12	controlled clinical trial.pt.	92449
13	Randomi?ed.ab.	413631
14	placebo.ab.	189534

15	clinical trials as topic.sh.	183863
16	randomly.ab.	291937
17	trial.ti.	183336
18	11 or 12 or 13 or 14 or 15 or 16 or 17	1155445
19	7 and 10 and 18	33

Notes: Lines 8 and 9 (combined at line 10) focus on the primary interventions relating to the research question as specified in the PICO. This search will identify any comparators to the interventions specified in the PICO where studies reporting RCTs exist in the bibliographic databases indicated for searching.

Estimated volume of studies to screen, when the Embase search is included, is approximately 200.

Vascular PICO

Research question 1: Should patients with dementia (and no stroke) and atrial fibrillation be treated with anti-coagulants?

Research question 2: Does systematical management of vascular risk factors in patients with dementia slow the progression of dementia ?

Database: MEDLINE
Host: Ovid
Data parameters: 1946 to present
Date searched: Thursday June 21st 2018
Search strategy:

#	Searches	Results
1	exp Dementia/	146709
2	(Dement$ or Alzheimer$ or Amnes$ or Parkinson$ or Huntington$ or lewy$ bod$ or pick$ disease or Posterior cortical atrophy or aphasia or (brain adj1 (disease$ or syndrome$)) or binswanger* or Progressive supranuclear palsy or Steele-Richardson-Olszewski syndrome or Frontotemporal disorder$ or Frontotemporal degeneration or Corticobasal degeneration or Corticobasal syndrome or cognitive disorder$ or Vascular cognitive).ti,ab,kw,ot.	316142
3	*Amnesia/	4649
4	exp Parkinsonian Disorders/	71220

5	*Huntington Disease/	8822
6	*Supranuclear Palsy, Progressive/	1685
7	1 or 2 or 3 or 4 or 5 or 6	348756
8	Atrial Fibrillation/	46653
9	((atrial adj3 fibrillat$) or (atrium adj3 fibrillat*) or (auricular* adj3 fibrillat*) or (irregular adj1 heart beat) or atrial arrhythmi*).ti,ab,kw,ot.	61100
10	8 or 9	70499
11	exp *Hypertension/	174602
12	(hypertension or hyper tension or (high adj (blood pressure or BP))).ti,ab,kw.	354520
13	11 or 12	395120
14	*Hypercholesterolemia/	15773
15	(hypercholesterolemia or (high adj cholesterol)).ti,ab,kw.	28245
16	14 or 15	36988
17	exp Diabetes Mellitus, Type 2/	114492
18	diabet$.ti,ab,kw.	553758
19	17 or 18	564225
20	10 or 13 or 16 or 19	978276
21	7 and 20	13027
22	randomized controlled trial.pt.	462372
23	controlled clinical trial.pt.	92449
24	randomized.ab.	413631
25	placebo.ab.	189534
26	clinical trials as topic.sh.	183863
27	randomly.ab.	291937
28	trial.ti.	183336
29	22 or 23 or 24 or 25 or 26 or 27 or 28	1155445
30	Epidemiologic studies/	7705
31	exp case control studies/	921330
32	exp cohort studies/	1749889
33	Case control.tw.	108264
34	(cohort adj (study or studies)).tw.	156202
35	Cohort analy$.tw.	6235
36	(Follow up adj (study or studies)).tw.	45130

37	(observational adj (study or studies)).tw.	81821
38	Longitudinal.tw.	205197
39	Retrospective.tw.	428891
40	Cross sectional.tw.	279445
41	Cross-sectional studies/	267434
42	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	2580155
43	29 or 42	3490164
44	21 and 43	3725

Estimated volume of studies to screen, when the Embase search is included, is approximately 8,000-9,000.

Systematic Medical Follow-Up PICO

Research question 1: Should home-living patients with dementia be offered systematic medical follow-up in a memory clinic setting?

Database: MEDLINE
Host: Ovid
Data parameters: 1946 to present
Date searched: Thursday June 21st 2018
Search strategy:

#	Searches	Results
1	exp Dementia/	146709
2	(Dement$ or Alzheimer$ or Amnes$ or Parkinson$ or Huntington$ or lewy$ bod$ or pick$ disease or Posterior cortical atrophy or aphasia or (brain adj1 (disease$ or syndrome$)) or binswanger* or Progressive supranuclear palsy or Steele-Richardson-Olszewski syndrome or Frontotemporal disorder$ or Frontotemporal degeneration or Corticobasal degeneration or Corticobasal syndrome or cognitive disorder$ or Vascular cognitive).ti,ab,kw,ot.	316142
3	*Amnesia/	4649
4	exp Parkinsonian Disorders/	71220
5	*Huntington Disease/	8822
6	*Supranuclear Palsy, Progressive/	1685
7	1 or 2 or 3 or 4 or 5 or 6	348756

8	(home or house or apartment or building).ti,ab,kw,ot.	326937
9	(memor$ adj3 clinic$).ti,ab,kw,ot.	3703
10	7 and 8 and 9	93

Notes: This search had initially been discussed as being limited to RCTs or observational studies Given the change in RQ in the task force meeting, and the low number of studies identified in MEDLINE, I would recommend screening without limitation to study design.

Estimated volume of studies to screen, when the Embase search is included, is approximately 400

Anti-Psychotics PICO

Research question 1: Should patients with dementia and agitation/aggressive behaviour be treated with atypical anti-psychotics compared to no pharmacological treatment?

Research question 2: Should patients with dementia and agitation/aggressive behaviour be treated with atypical anti-psychotics compared to haloperidol?

Research question 3: Should treatment with antipsychotics be routinely discontinued?

Database: MEDLINE
Host: Ovid
Data parameters: 1946 to present
Date searched: Thursday June 21st 2018
Search strategy:

#	Searches	Results
1	exp Dementia/	146709
2	(Dement$ or Alzheimer$ or Amnes$ or Parkinson$ or Huntington$ or lewy$ bod$ or pick$ disease or Posterior cortical atrophy or aphasia or (brain adj1 (disease$ or syndrome$)) or binswanger* or Progressive supranuclear palsy or Steele-Richardson-Olszewski syndrome or Frontotemporal disorder$ or Frontotemporal degeneration or Corticobasal degeneration or Corticobasal syndrome or cognitive disorder$ or Vascular cognitive).ti,ab,kw,ot.	316142
3	*Amnesia/	4649
4	exp Parkinsonian Disorders/	71220
5	*Huntington Disease/	8822
6	*Supranuclear Palsy, Progressive/	1685
7	1 or 2 or 3 or 4 or 5 or 6	348756
8	exp Antipsychotic Agents/	115288

9	(antipsychotic* or "anti-psychotic*" or tranquilizer*).ti,ab.	38400
10	(Droperidol or Flupentixol or Fluphenazine or Haloperidol or Pimozide or Prochlorperazine or Thioproperazine or Trifluoperazine or Zuclopenthixol or Loxapine or Molindone or Perphenazine or Thiothixene or Chlorpromazine or Chlorprothixene or Levomepromazine or Mesoridazine or Periciazine or Promazine or Thioridazine).ti,ab.	40608
11	8 or 9 or 10	138094
12	7 and 11	8076
13	randomized controlled trial.pt.	462372
14	controlled clinical trial.pt.	92449
15	randomized.ab.	413631
16	placebo.ab.	189534
17	clinical trials as topic.sh.	183863
18	randomly.ab.	291937
19	trial.ti.	183336
20	13 or 14 or 15 or 16 or 17 or 18 or 19	1155445
21	12 and 20	1148

Treatment of pain PICO

Research question 1: In patients with dementia, should opioids be discontinued?

Research question 2: Should behavioral symptoms in patients with dementia be treated with mild analgesics?

Database: MEDLINE
Host: Ovid
Data parameters: 1946 to present
Date searched: Thursday June 21st 2018
Search strategy:

#	Searches	Results

1	exp Dementia/	146709
2	(Dement$ or Alzheimer$ or Amnes$ or Parkinson$ or Huntington$ or lewy$ bod$ or pick$ disease or Posterior cortical atrophy or aphasia or (brain adj1 (disease$ or syndrome$)) or binswanger* or Progressive supranuclear palsy or Steele-Richardson-Olszewski syndrome or Frontotemporal disorder$ or Frontotemporal degeneration or Corticobasal degeneration or Corticobasal syndrome or cognitive disorder$ or Vascular cognitive).ti,ab,kw,ot.	316142
3	*Amnesia/	4649
4	exp Parkinsonian Disorders/	71220
5	*Huntington Disease/	8822
6	*Supranuclear Palsy, Progressive/	1685
7	1 or 2 or 3 or 4 or 5 or 6	348756
8	*Analgesics, Opioid/	25311
9	(narcotic* or opioid* or morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).ti,ab,kw,ot.	154287
10	Narcotics/	15932
11	Morphine/	36799
12	Buprenorphine/	4579
13	Codeine/	4326
14	Dextromoramide/	359
15	Diphenoxylate/	223
16	Dextropropoxyphene/	1453
17	Alfentanil/	1638
18	Fentanyl/	12728
19	Methadone/	11587
20	Nalbuphine/	642
21	Opium/	1947
22	Oxycodone/	1930
23	Pentazocine/	2211

24	Meperidine/	5611
25	Phenazocine/	510
26	Hydrocodone/	543
27	hydromorphone/	1176
28	Levorphanol/	601
29	Oxymorphone/	482
30	butorphanol/	1034
31	Sufentanil/	1714
32	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	176030
33	randomized controlled trial.pt.	462372
34	controlled clinical trial.pt.	92449
35	randomized.ab.	413631
36	placebo.ab.	189534
37	clinical trials as topic.sh.	183863
38	randomly.ab.	291937
39	trial.ti.	183336
40	33 or 34 or 35 or 36 or 37 or 38 or 39	1155445
41	7 and 32 and 40	241

Estimated volume of studies to screen, when the Embase search is included, is approximately 500

Appendix E

EAN Guideline on medical management of dementia

Treatment of epilepsy in dementia

Topic coordinator:
Christer Nilsson

Senior advisor
Giovanni B. Frisoni

RQ 1. Should patients with dementia and 1 or more seizures after diagnosis be treated with either levetiracetam/lamotrigine or carbamazepine/phenytoin/valproate?

Population	Patients with dementia and 1 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*

Appendix F

EAN Guideline on medical management of dementia

Management of vascular risk factors

Topic coordinator
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RQ1. Should patients with dementia (and no stroke) and atrial fibrillation be treated with anti-coagulants?

Population	Patients with dementia and atrial fibrillation and no previous stroke or TCI	
Intervention	Treatment with NOACs or warfarin	
Comparator	No treatment with NOACs or warfarin	
Outcome	1. Major hemoragic events	*Critical*
	2. Global cognitive function	*Important*
	3. Mortality	*Important*
	4. Ischemic vascular event	*Critical*

RQ 2. Does systematical management of vascular risk factors in patients with dementia slow the progression of dementia?

Population	Patients with dementia	
Intervention	Systematic management of vascular risk factors (Hypertension, hypercholesterolemia, diabetes mellitus type 2)	
Comparator	Usual care	
Outcome	1. Institutionalisation	*Important*
	2. Global cognitive function	*Critical*
	3. Mortality	*Critical*
	4. ADL	*Important*

Appendix G

EAN Guideline on medical management of dementia

Systematic medical follow-up in dementia

Topic coordinator
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Senior Coordinator
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RQ 1. Should patients with dementia be offered systematic medical follow-up in a memory clinic setting?

Population	Home-living (non-istititonalised) 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. Institutionalisation	*Important*
	2. Caregiver burden	*Important*
	3. Acute hospital admissions	*Important*
	4. ADL	*Critical*

Appendix H

EAN Guideline on medical management of dementia

Treatment with antipsychotics in dementia

Topic coordinator
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RQ 1. Should patients with dementia and agitation/aggressive behaviour be treated with atypical anti-psychotics compared to no pharmacological treatment?

Population	Patients with dementia and agitation/aggressive behavior	
Intervention	Treatment with aripripazole, zoleptil, olanzapine, quetiapin, risperidone or clozapine	
Comparator	No pharmacological treatment	
Outcome	1. Mortality	*Critical*
	2. Agitation/Aggression	*Important*
	3. Global cognitive function.	*Important*
	4. Serious adverse events	*Critical*
	5. Caregiver burden	*Important*

RQ 2. Should patients with dementia and agitation/aggressive behaviour be treated with atypical anti-psychotics compared to haloperidol?

Population	Patients with dementia and agitation/aggressive behavior	
Intervention	Treatment with aripripazole, zoleptil, olanzapine, quetiapin, risperidone or clozapine	
Comparator	Haloperidol	
Outcome	1. Mortality	*Critical*
	2. Agitation/Aggression	*Important*
	3. Global cognitive function.	*Important*
	4. Serious adverse events	*Critical*
	5. Caregiver burden	*Important*

RQ 3. Should treatment with antipsychotics be routinely discontinued?

Population	Patients dementia who are currently being treated with anti-psychotics	
Intervention	Discontinuation of antipsychotics	
Comparator	Continuation of treatment	
Outcome	1. Mortality	*Critical*
	2. Neuropsychiatric symptoms	*Important*
	3. Global cognitive function.	*Important*
	4. Serious adverse events	*Critical*
	5. Caregiver burden	*Important*

Appendix I

EAN Guideline on medical management of dementia

Treatment of pain in dementia

Topic coordinatior:
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RQ 1. In patients with dementia, should opioids be discontinued?

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	*Critical*
	4. Pain	*Important*

	5. Neuropsychiatric symptoms	*Important*

RQ 2. Should behavioral symptoms in patients with dementia be treated with mild analgesics?

Population	Patients with dementia and behavioural 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*