Evidence-based medicine in geriatrics

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Evidence-based medicine in geriatrics

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Table Of Contents

General Introduction

Current status of evidence in the care for older people

The ageing population and increasing longevity pose numerous challenges on health care professionals. Especially in more developed regions, the number of older people is growing at a faster rate than ever before. Almost 33% of the population in these regions is projected to be 60 years or over, up from 22% in 2009 (1). Older people are heterogeneous in terms of illness severity, functional status, prognosis, personal priorities and risk of adverse events. In addition, they often have a combination of two or more chronic diseases, defined as multimorbidity (2). Multimorbidity is associated with frailty, higher rates of death, premature disability, adverse drug effects, institutionalization, higher use of healthcare resources and poorer quality of life (3). Providing optimal care for these group of patients is complicated and should ideally be based on solid evidence derived from well-performed clinical studies investigating end-points that are relevant for the population, combined with the physician's experience and the patients' preferences and situation. The integration of individual clinical expertise with the best available scientific evidence and patients' preferences is called 'Evidence-based Medicine' (EBM) (4;5).

Since its introduction in 1992, EBM has become more and more implemented into clinical practice. However, the generation of clinically applicable research for evidence-based practice in geriatric medicine is still difficult for several reasons. Evidence specifically tailored to the clinical care of older people with multimorbid diseases is limited because they are underrepresented in or excluded from clinical research (6;7). As a result, many older people are treated according to clinical practice guidelines that are based on evidence retrieved from studies conducted in non-representative younger patients or healthy older persons. It is questionable whether optimal care is provided to this category of patients, because it is usually not realistic to believe that evidence created for patients in their fifties also holds true for 80-year-old patients (8). In addition, many clinical practice guidelines focus on the management of a single disease. As a consequence, they are difficult to apply to older people with multimorbidity (9;10).

What are the reasons for the undesirable fact that older people are proportionately underrepresented or even excluded from most clinical trials? In many cases age limits are set without justification (7;11). Often, trials automatically exclude older people, because patients with co-morbidities, drug use or decision incapacity are ineligible (12). Furthermore, when an intervention is studied in people with varying multiple chronic conditions, it becomes more difficult to demonstrate an effect, because with increasing heterogeneity the chance of isolation of an effect decreases. This might refrain researchers from designing trials for the heterogeneous older population (8). Another reason for excluding older people is the fear they are less capable of adhering to research protocols, thereby increasing the number of drop-outs in their study (13). In addition, researchers may have concerns about older people recalling information (14) or their ability to provide a legal informed consent (15).

Even when researchers allow inclusion of older patients with or without multimorbidity in clinical trials it remains challenging to find appropriate numbers of participants to test a representative sample of the target population (13). However, the population imperative, the demonstrated lack of inclusion of older adults in clinical trials, and the consequent lack of evidence that is directly applicable to care and policy decisions regarding older adults should lead to a change in researchers' attitude towards the role of age as a study exclusion criterion (8) and should encourage scientists to search for alternative research methods to generate evidence for the growing group of older patients.

Aim and content of this thesis

This thesis consists of several different research projects, centred around the theme 'evidence-based medicine in geriatrics'. The general aim of this thesis was to better disseminate EBM for geriatric medicine by making the available evidence more accessible to clinicians and to identify opportunities to increase the relevance of aggregated data, tailored to geriatric patients, for making healthcare decisions about older patients. In addition, we aimed to generate evidence relevant for geriatric patients by performing a randomized controlled trial (RCT) in a representative older population and by investigating alternative methods for generating evidence for this group. The first part of this thesis consists of challenges around the search for evidence and aims to make evidence better available to geriatric clinicians by systematically summarizing research results with innovative review methodologies. The second part investigates ways to generate evidence tailored for the treatment of geriatric patients, by investigating different methods to better adapt the available research findings to patients with limited life expectancy, by initiating and coordinating a clinical trial with participation of representative elderly patients and by investigating barriers and motivators of older people towards participation in a clinical trial.

The cornerstone of EBM is that clinicians should be able to find answers to clinical questions in the available scientific literature themselves, as knowledge rapidly gets out of date and the body of evidence expands in a rapid speed. After identifying the research question, the next step in EBM is to search for relevant literature. In **Chapters 2 and 3**, we present our search filters that were developed to simplify efficient searching in MEDLINE for relevant literature concerning geriatric medicine. Our search filters are helpful tools for physicians who have limited time. These filters were developed and tested according to formal, generally accepted validation methods.

Chapters 4 and 5 cover two different methods to summarize available literature on a specific topic relevant for geriatric patients using innovative systematic methods thereby focussing on end-point that are relevant for the geriatric patient. **Chapter 4** is a systematic review on prognostic factors. Prognostication is important in geriatrics, as clinical management decisions for this population necessitate the evaluation of prognosis to inform patient preferences and to adequately assess risks, burdens, and benefits, including remaining life expectancy, functional disability, and quality of life (9). This

chapter systematically reviews what the pre-arrest predictors of survival are from out-of-hospital cardiac arrest in an older population. In addition to the end-point survival, we also incorporated patient-relevant outcomes, such as functional capacity, cognitive functioning and quality of life of survivors. Focussing on these patient-important outcomes too is important for goal-oriented patient care (16). In this chapter, we formulated recommendations for future studies that investigate outcomes of cardiopulmonary resuscitation with regard to reporting data and pre-arrest factors, in order to make future meta-analyses of studies on this topic easier to perform and to make sure that the available body of evidence is better applicable to older patients. **Chapter 5** describes a scoping review of systematic reviews that address pharmacological treatment of dementia. While a systematic review focuses on retrieving an answer to a well-defined question, a scoping review 'maps' the relevant literature in a complete field of interest and describes only the main findings; by doing so, gaps in the available literature can be identified easily (17). This is especially useful for fields in which much literature is available, like in the field of dementia research. In addition, we investigated whether outcomes relevant for the older patient were reported as well. In the light of their multiple chronic comorbidities, older people with dementia may not benefit from research that only describes mortality and morbidity as outcomes. Patient-relevant outcomes, such as symptom burden, functional capacity, and self-rated health should be investigated too (16;18). In **Chapter 6**, we investigated systematically whether patients with cognitive impairment were included in studies on the pharmacological prophylaxis or treatment of delirium, a problem present in >60% of the patients with cognitive impairment. In patients with cognitive impairment, underlying pathophysiological mechanisms, such as imbalances in various neurotransmitter systems or the effects of inflammation on the brain via cytokines, may be different compared to patients without cognitive impairment. These differences may also cause variations in the effects and side effects of medications (19). Even in the case the correct age groups are investigated, it is possible that the results of these trials cannot be extrapolated directly to patients that usually develop delirium, namely patients with cognitive impairment. Therefore, we also investigated the motivations for excluding patients with cognitive impairment. Even though patients with cognitive impairment or dementia in some occasions are able to give consent (20), they are often excluded. When they lack this capacity, there are guidelines with regard to consent procedures, such as asking consent by proxy (8).

In the second part of this thesis, we investigated alternative ways to generate solid evidence for geriatric patients. Results from intervention studies cannot always easily be applied to geriatric patients with limited life expectancy, as it is possible that they will not live long enough to benefit from newly started preventive medication. **Chapter 7** describes a novel method to estimate the time-to-benefit (TTB) for preventive drugs with the Statistical Process Control (SPC). The TTB is defined as the estimate of time until a treatment becomes significantly effective in a group of patients. For physicians, it is important to know the TTB because it is possible that older patients will not live long

enough to benefit from preventive medication, whereas they are at risk for harmful side effects. This can support treatment decisions. Currently, there is no generally accepted method to define the TTB. SPC is an innovative method that shows the TTB in graphs that are easy to interpret. In **Chapter 8** we looked at another promising and innovative method for getting aggregating data for older patients: meta-analyzing the 'raw' or individual patient data (IPD). The number of older patients enrolled in RCTs is often insufficient to perform meaningful subgroup analyses. Because the sparsely included older people in original trials are combined into a database and meta-analyzed, new evidence can be achieved without performing new RCTs**.** Furthermore, especially in the field of geriatrics, performing a traditional meta-analysis of original studies can be difficult due to heterogeneity of all different kind, such as heterogeneity of studied populations; different aims of included studies; no consistent categorization scheme for interventions and minimal reporting of intervention details; lack of details about control group care; and inconsistent reporting of types of outcomes and analyses of different moments in time (21). With a meta-analysis of IPD, it is possible to compare studies that employed different instruments to obtain comparable outcomes by redefining variables, which is especially relevant for patient-relevant outcomes, such as quality of life and functionality. We investigated the inclusion of older populations in IPD reviews available through MEDLINE. In addition we explored whether these IPD reviews report different conclusions for the older group compared to younger patients.

In the 'pyramid of evidence' an RCT is considered as the best instrument to evaluate the efficacy of an intervention and therefore, is rated as the highest quality of evidence, but relatively few RCTs are available for the older patients (22). In **Chapter 9** we described the results of a randomized, placebo-controlled double blind trial that we initiated, coordinated and performed that studied the efficacy of acetaminophen in self-reported sleep problems in a group of older patients. In geriatric clinical practice, we noticed that many older community dwelling patients use acetaminophen for chronic sleep problems without having specific underlying pain complaints. Sleep problems are highly prevalent and current therapies have negative adverse effects such as impact on cognitive functioning and driving. Therefore, there is a need for an effective and safer treatment with fewer side effects. In **Chapter 10**, we studied the barriers and facilitators towards participation in an RCT that investigated the efficacy of melatonin in the prevention of post-operative delirium in older hip fracture patients, in order to provide guidance and suggestions for researchers to improve the participation of seniors in trials and to reduce their burden. In this study we systematically investigated the clinical characteristics of both older patients who gave their consent for participation and those who did not, as well as a number of potential barriers and motivators, such as the moment of asking, the blood test and the influence of care givers on the willingness to give consent. Finally, in the general discussion, in **Chapter 11,** we elaborate on the observed results and offer directions for future research in older patients.

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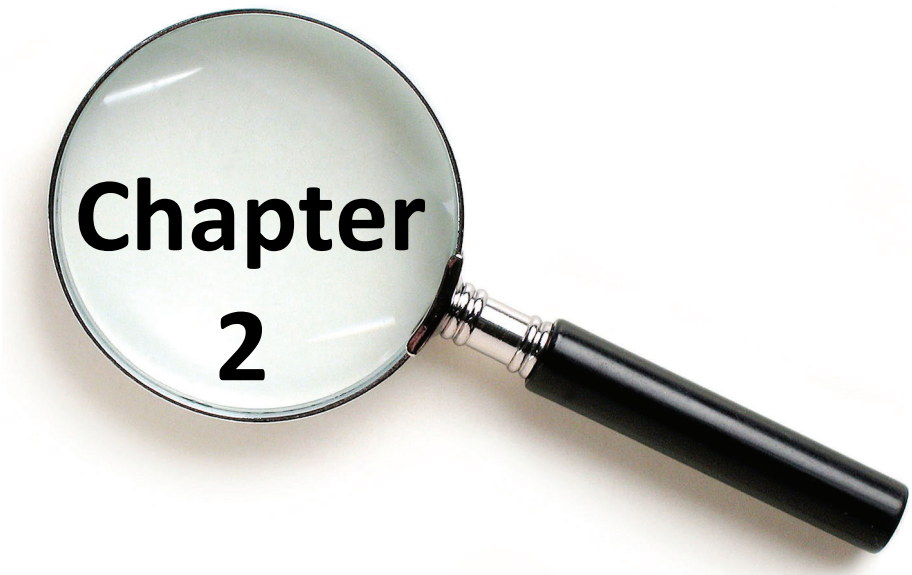

Search filters to identify geriatric medicine in MEDLINE

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Chapter 2

Abstract

Objectives: To create user-friendly search filters with high sensitivity, specificity and precision to identify articles concerning geriatric medicine in MEDLINE.

Design: We used a diagnostic test assessment framework. We created a reference set of 2,255 articles by hand searching 22 biomedical journals in MEDLINE and labeled each article as relevant, not relevant or possibly relevant for geriatric medicine. From the relevant articles, we identified search terms to compose different search strategies. We compared the articles retrieved by the various search strategies with articles from the reference set as the index test to create the search filters.

Measurements: Sensitivity, specificity, precision, accuracy and number-needed-to read (NNR) were calculated by comparing the results retrieved by the different search strategies with the reference set.

Results: The most sensitive search filter had a sensitivity of 94.8%, a specificity of 88.7%, a precision of 73.0% and an accuracy of 90.2%. It had a NNR of 1.37. The most specific search filter had a specificity of 96.6%, a sensitivity of 69.1%, a precision of 86.6% and an accuracy of 89.9%. It had a NNR of 1.15.

Conclusion: Our geriatric search filters simplify searching for relevant literature and, therefore, contribute to a better evidence-based practice. The filters are useful to both the clinician who wants to find a quick answer to a clinical question and to the researcher who wants to find as many relevant articles as possible without retrieving too many irrelevant articles.

Introduction

The ageing population is increasing demand on healthcare. Geriatric patients often have multiple chronic conditions, use many medications and may suffer from cognitive and functional impairments. A study about prevalence of morbidities in the elderly showed that 82% of patients aged 65 and over had at least one chronic condition; 24% had four or more conditions (1). Due to deteriorating organ functions they are prone to medication-related side effects (2). Consequently, care of the elderly is complicated. To provide the best care, doctors need to be able to find relevant information quickly and easily.

Information specific to geriatric patients is hard to find for several reasons. Geriatric medicine overlaps with, among others, psychiatry, internal medicine and neurology and therefore, information relating to geriatrics is published in a wide range of journals. In addition to that, the amount of available information is increasing at a rapid rate, and time for searching is limited. Even though bibliographic databases often provide tools to improve the performance of searching (e.g. Medical Subject Heading (MeSH) terms in MEDLINE), using these correctly can be challenging. Moreover, indexing in MEDLINE is not always consistent (3-5). Furthermore, there is a time lag between articles being published and being indexed with MeSH terms in MEDLINE, with the result that recently published articles will not be found when only MeSH-terms are used.

With a search strategy or 'filter' focused on geriatrics, clinicians, policy-makers, librarians and information specialists would be able to find the answers to clinical questions more quickly than with a general search in the whole database. Searchers could, for example, combine 'cardiac failure' with a geriatrics search filter to improve the precision of retrieving articles relevant to the case at hand.

Researchers have previously developed MEDLINE search filters for other branches of medicine. Search filters consist of MeSH terms and text words in titles and abstracts that are related to the subject of the intended search. Iansavichus et al. developed search filters for renal information for Embase (6), Gehanno and colleagues created a search filter to identify studies on return-to-work (7) and Boluyt et al. tested the sensitivity and precision of search filters for retrieving child health systematic reviews (8).

In 2006, Kastner et al. developed search strategies to identify relevant articles for several age-specific categories (9). These strategies were constructed from search terms concerning age groups, whereas we aim to create search filters that identify not only articles on older people, but also geriatric topics in general.

The objective of this study was to develop systematically and test various search strategies in order to create search filters to identify articles concerning geriatric medicine in MEDLINE and to test their operating characteristics, namely the sensitivity, specificity, precision and accuracy. Sensitivity is defined as the number of retrieved records which are relevant, divided by the total number of relevant records in the reference set. The relevant records that are missed are referred to as false negatives. A highly sensitive search will result in few relevant records being missed. Specificity is defined as the number of correctly not identified irrelevant records, divided by the total number of

irrelevant records in the reference set. Consequently, a highly specific search will result in few irrelevant records being retrieved. The irrelevant records that are retrieved are referred to as false positives. Precision is defined as the number of relevant records retrieved, divided by the total number of records retrieved. This is also known as positive predictive value. The accuracy is defined as the number of records that is dealt with correctly by the search filter. The number-needed-to-read (1/precision) is a measure of the usability of the filter, because it indicates how many records a searcher must screen for each relevant record retrieved.
Our research questions were: (a) Which is the most specific filter? (b) Which is the most sensitive filter? How usable are these search filters (low number-needed-to-read (NNR))? Also, we compared the operating characteristics of our search filters with the only other existing age-specific search filter which we were aware of, the one developed by Kastner et al (9).

Methods

Construction of the reference set
We created the search filters for MEDLINE using the PubMed interface because this database and interface is freely accessible and widely used. We used a diagnostic test analytic framework to develop and test the geriatric search filters (6). To assess the performance of the search filters, we compared their retrieval with a reference standard compiled by hand-searching journal articles. We treated the search filters as diagnostic tests for relevant studies, and the manual review of the literature was considered as the 'gold standard' or reference set (6;10). This reference standard consisted of articles from high impact factor journals published in the UK and the USA, chosen after consulting several geriatricians, neurologist and psychiatrists. We included articles from these journals published in the last quarter of 2009 to lessen the risk that not all articles in the reference set were indexed in MEDLINE at the time that the searches were conducted.
Two of the authors (EvdG and BvM) hand-searched these journals independently of each other, and scored each article as 'relevant', 'not relevant' or 'possibly relevant' to geriatric medicine. Disagreements were discussed with a third author (LH). We categorized articles as relevant for geriatric medicine if they comprised topics that concerned the so-called 'geriatric giants' (incontinence, immobility, instability and cognitive impairment (11;12)), described a condition specific to old age, or were on a group of patients whose mean age was over 70. There were some articles that were not easy to classify as relevant or not. These were articles on a general topic that was of some relevance for geriatrics and articles, for example, about studies that, among others, included patients aged above 70. We labeled these articles as 'possibly relevant'. The remaining articles were labeled as not relevant for geriatric medicine.
The reference set was alphabetized by first author's family name, and we split it halfway into a development set and a validation set. The development set was used to find

discriminating text words, phrases and MeSH-terms and to test the operating characteristics of the strategies. The validation set was used to test the strategies' performance independently.
After splitting the set, we excluded the publication type 'letters', because they usually refer to a published original study already identified by the search strategies. This prevented a false increase of the prevalence of relevant articles in the reference set; thereby overestimating the precision; when the prevalence of relevant information in a database is high, the positive predictive value (precision) of finding relevant information is also high. All other publication types were included, so the reference set contained various article types that were labeled as relevant, possibly relevant or not relevant.

Creating search strategies
To create robust search filters, relevant text words and MeSH-terms had to be chosen. Two different approaches were used to find discriminating search terms. First, using the program PubReminer (13) a frequency analysis was performed to find the most frequently occurring single-term text words and MeSH-terms within the development set, in both the relevant and the not relevant articles. This tool was originally developed to refine literature searches by providing the most frequently used keywords in the retrieved articles. In short, PubReminer submits a user query to PubMed and retrieves the full records for all citations matching the query. From these records publication year, journal title, first author, MeSH terms, substances, country and text words within title and abstract were extracted and used for the generation of frequency tables. These frequency tables are then presented in an interactive way allowing for adaptation of the original query based on the frequency results.
Second, with the program TerMine from the National Centre for Text Mining (NaCTem) (14) we analyzed the frequency of phrases within titles and abstracts.
By comparing the most frequently occurring text words, phrases and MeSH terms in both the relevant and the not relevant records, we compiled a list of discriminating search terms to construct the test search filters. A search term was considered discriminating either when it occurred exclusively in the list of relevant articles, or when it occurred five times more in the relevant records than in the records that were not relevant. We chose the factor five, because this was a good cut-off in the results. Finally, we had a list of discriminating text words, a list of discriminating MeSH-terms and a list of discriminating phrases. These three lists were combined with the Boolean operator 'OR' to create a search filter with high sensitivity. The search filter with high specificity consisted of search terms identified by the frequency analysis that occurred exclusively in the list of relevant records. To improve the sensitivity, we added search terms that were not exclusively in the list of relevant records, but occurred more than 10 times more in the relevant records than in the records that were not relevant.

Filter testing

With a spreadsheet program we compared the retrieved results of the different search strategies with the labeled records from the development set. Then we calculated the operating characteristics sensitivity, specificity, precision and accuracy (Table 1).

Firstly, the 'possibly relevant' articles were classified as 'not relevant' records that the search strategies should not identify.

We wanted our search strategies to have either the sensitivity or the specificity above 80%. Subsequently, the strategies were applied to the validation set to test their performance independently and to compare their operating characteristics with those of the development set.

Then we labeled the possibly relevant articles as relevant records that the search filters should identify and tested the operating characteristics of the search filters a second time.

Finally, we compared the performance of our search filters with the age-specific search strategies for geriatric medicine developed by Kastner et al. Therefore, we tested their search strategy with best optimized sensitivity and specificity (Aged.sh, not exploded) in our reference set, and compared the operating characteristics of this search strategy with our search filter with highest specificity or sensitivity.

Table 1: Calculation of a search filter's operating characteristics

		Reference set	
		Article meets criteria (relevant)	Article does not meet criteria (not relevant)
Search filter	Article identified	a (true positives)	b (false positives)
	Article not identified	c (false negatives)	d (true negatives)

Sensitivity = a / (a+c), Specificity = d / (b+d), Precision = a / (a+b), Accuracy = (a+b) / (a+b+c+d), Number-needed-to read = 1 / Precision

Results

The reference set consisted of 3,012 articles from 22 journals. After exclusion of the letters, 2,255 articles remained (Table 2).

A total of 1,062 formed the development set, and 1,195 formed the validation set. In total, 567 (25.1%) of the articles contained information relevant to geriatric medicine according to our criteria, 142 articles (6.3%) were classified as possibly relevant and 1,546 (68.6%) articles remained that were classified as not relevant. There were some articles in the geriatric medicine section of articles that were not relevant. This can be explained because the majority of these concerned aging studies in animals.

The frequency analysis with PubReminer yielded a total of 20 discriminating, free-text search terms and 10 discriminating MeSH terms. With TerMine, we found 5 sets of multi-word terms. Using these terms, we constructed the sensitive search filter. This search filter had a sensitivity of 92.0 % and a specificity of 86.9% in the development set with similar results in the validation set. It identified 254 out of 276 relevant records correctly and missed only 22 records (false negatives). It had a NNR of 1.40 (Table 3a).

Table 2: Selected journals and number of articles included in the reference set (Oct-Dec 2009)

	Name of journal	Not relevant	Relevant	Possibly relevant	Total no.	(% of reference set)
General medicine	New Eng J Med	207	14	18	239	10.6
	BMJ	312	20	7	339	15.0
	JAMA	165	15	11	191	8.5
	Ann Int Med	79	9	11	99	4.4
	Lancet	233	11	12	256	11.4
Geriatric medicine	J Am Geriatr Soc	7	102	2	111	4.9
	Age Ageing	1	49	2	52	2.3
	Drugs Aging	0	9	0	9	0.4
	J Gerontol A Biol Sci Med Sci	19	58	2	79	3.5
	Int Psychogeriatr	3	63	0	66	2.9
Neurology	Brain	82	17	12	111	4.9
	Ann Neurol	47	5	5	57	2.5
	Neurology	135	42	23	200	8.9
	Arch Neurol	38	18	8	64	2.8
	J Neurol Neurosurg Psychiatry	71	26	21	118	5.2
Psychiatry	Am J Psychiatry	58	4	1	63	2.8
	Am J Geriatr. Psychiatry	3	28	1	32	1.4
	Arch Gen Psychiatry	29	3	1	33	1.5
	Br J Psychiatry	45	2	1	48	2.1
	Psychiatry	6	0	0	6	0.3
	Int J Geriatr Psychiatry	6	58	3	67	3.0
	J Geriatr Psychiatry Neurol	0	14	1	15	0.7
	Total (% of total)	1,546 (68.6)	567 (25.1)	142 (6.3)	2,255	100%

The search filters can be found in the appendix. The search filter with the highest specificity was constructed of search terms that were found exclusively in the list of relevant records. This filter had a specificity of 96.6% and a sensitivity of 69.1%, with a number-needed-to-read of 1.15 with similar results in the validation set. This filter incorrectly identified only 31 of 784 not relevant records (false positives). To improve the sensitivity, we added several search terms to the search filter. The selected search terms all occurred at least 10 times more often in the relevant set compared to the not relevant set. By doing this, we improved the sensitivity to 74.6% at the cost of a slightly lower specificity (95.7%). Also, these operating characteristics were similar in the validation set (Table 3a).

Thereafter, we compared the operating characteristics of our search strategies with those of the best optimized age-specific search filter developed by Kastner et al. (9). In our reference set, their filter had a lower sensitivity (81.6%) and specificity (79.9%), compared to the performance in their original reference set (sensitivity 93.6%, specificity 82.7%). In our reference set, our best optimized filter (no 1.) had better sensitivity, specificity and precision than Kastner's (Table 3a).

Finally, we analyzed the performance of the strategies in case they retrieved not only the indisputably relevant records but also the articles that were labeled as 'possibly relevant'. By doing this the sensitivity of the strategies slightly decreased, while in contrast the specificity increased slightly or remained the same. Still, our search strategies remain usable (Table 3b).

Table 3a: Operating characteristics of our best performing search strategies compared with each other and with Kastner's best search filter. The search filter that yields the best optimization of sensitivity and specificity is search filter 1

	Search filter							
Operating characteristics (95% CI)	**No 1. Most sensitive* (best optimized)**		**No 2. Most specific***		**No 3. Specific search filter with increased sensitivity***		**No 4. Best search strategy Kastner et al.§**	
	D†	V‡	D	V	D	V	D	V
Sensitivity (%)	92.0 (88.8-95.2)	94.8 (92.3-97.4)	69.6 (64.1-75.0)	69.1 (63.8-74.4)	74.6 (69.5-79.8)	75.3 (70.3-80.2)	81.6 (77.3-86.4)	82.1 (77.1-86.5)
Specificity (%)	86.9 (84.5-89.2)	88.7 (86.7-90.8)	96.0 (94.7-97.4)	96.6 (95.4-97.8)	95.7 (94.2-97.0)	96.0 (94.6-97.2)	79.9 (77.2-82.8)	84.1 (81.7-86.5)
Precision (%)	71.1 (66.4-75.8)	73.0 (68.5-77.5)	86.1 (81.6-90.6)	86.6 (82.3-91.0)	85.8 (81.4-90.2)	85.5 (81.2-89.9)	58.9 (53.9-63.7)	62.4 (57.6-67.3)
Accuracy (%)	88.2 (86.3-90.1)	90.2 (88.5-91.9)	89.2 (87.0-91.3)	89.9 (88.2-91.6)	90.2 (88.1-92.3)	90.9 (89.2-92.5)	80.3 (77.9-82.7)	83.6 (81.5-85.7)
NNR	1.41 (1.32-1.50)	1.37 (1.29-1.46)	1.16 (1.10-1.23)	1.15 (1.10-1.22)	1.17 (1.11-1.22)	1.17 (1.11-1.23)	1.70 (1.57-1.85)	1.60 (1.49-1.74)

* See appendix / †D=development set, / ‡V= validation set / §Aged.sh

Table 3b: Operating characteristics of our best performing search strategies with the 'possibly relevant' articles labeled as 'relevant'

	Search filter							
Operating characteristics (95% CI)	**No 1. Most sensitive* (best optimized)**		**No 2. Most specific***		**No 3. Specific search filter with increased sensitivity***		**No 4. Best search strategy Kastner et al.§**	
	D†	V‡	D	V	D	V	D	V
Sensitivity (%)	79.3 (71.1-83.5)	84.9 (81.2-88.6)	56.9 (51.8-62.1)	58.1 (53.0-63.2)	61.2 (56.1-66.3)	64.0 (59.0-68.9)	79.1 (74.9-83.3)	78.2 (73.2-82.5)
Specificity (%)	89.1 (86.8-91.4)	91.3 (89.4-93.2)	96.6 (95.6-98.2)	97.1 (96.0-98.3)	96.6 (95.3-97.9)	96.8 (95.6-98.0)	85.3 (82.7-87.9)	87.7 (85.5-89.9)
Precision (%)	78.4 (71.2-82.7)	80.6 (76.6-84.6)	90.1 (86.2-94)	89.7 (85.7-93.6)	90.0 (86.2-93.8)	89.5 (85.7-93.2)	72.9 (68.5-77.4)	73.1 (68.7-77.5)
Accuracy (%)	85.8 (83.8-87.9)	89.4 (87.6-91.1)	83.6 (81.4-85.8)	85.4 (83.4 -87.4)	84.8 (82.7-87.0)	86.9 (85.0-88.9)	83.2 (81.0-85.5)	84.9 (82.8-84.9)
NNR	1.28 (1.21-1.35)	1.24 (1.18-1.30)	1.11 (1.06-1.16)	1.12 (1.07-1.17)	1.11 (1.07-1.16)	1.12 (1.07-1.17)	1.37 (1.29-1.46)	1.37 (1.29-1.46)

* See appendix / †D=development set / ‡V= validation set / §Aged.sh

Discussion

Because of its high sensitivity (94.8%), our most sensitive search filter (no 1, see appendix) is appropriate for the clinician or researcher who wishes to find as much relevant information as possible without missing too many articles. As the NNR is low (1.37) the search filter is also user-friendly.

The filter with high specificity (no 2, see appendix) has a higher than expected specificity (96.6%) with a somewhat lower NNR (1.15). Therefore, this search filter is more suitable for the physician who has limited time and needs a quick answer to a clinical question. It depends on the purpose of the searcher which filter is best to use.

In our reference set, the search strategy of Kastner et al. had a lower performance than in their original reference set. This is probably because of different inclusion criteria for relevant articles in our reference set. Kastner et al only included articles only that concerned patients in the age category of choice, while we included articles that were more specific for geriatric medicine. These articles were probably not found by the Kastner search filter.

Our most sensitive search filter performed better than that of Kastner et al. in our reference set. In the original article, the reported precision of Kastner's search filter was lower than in our reference set. This was to be expected, because their reference set contained a lower percentage of articles relevant to geriatric medicine (6.7%) than ours (25%). When our search filter would be used in the complete MEDLINE database, the precision will be lower too, because in MEDLINE also there is a lower percentage of geriatric information. This automatically lowers the positive predictive value of finding relevant information.

Furthermore, we used two different cut-offs for the classification 'relevant' (true positive search result) which is reflected in the variability of the sensitivity and specificity of the search filters. When 'possibly relevant' records were re-classified into 'relevant', the criteria for relevancy became broader and the criteria for irrelevancy became stricter. This resulted in a decreased sensitivity (more false negative search hits) and an increased specificity. After re-classifying the 'possibly relevant' records as 'relevant', the performance of the Kastner filter and ours was more comparable.

Which search strategy is best to use depends on the aim of the search. In geriatrics, it is more useful to use our filter because it is more suitable to find information on geriatric topics in general. However, if the aim of the search is to find articles that include elderly people directly or indirectly, the search strategies of Kastner et al. are usable too.

Our study has a number of strengths. Because we developed the reference set after consulting specialists, we enhanced the chance that the search terms and Mesh terms we used are relevant for geriatrics. In addition, systematically searching for suitable search terms to construct the search filters improves the operating characteristics of the search filters and thereby the reliability. Furthermore, splitting of the reference set enabled us to test the search filter a second time; it appeared that the retrieval performance of the search filters remained excellent in an independent set of articles.

On the other hand, these strategies have some limitations that are worth noting. We assumed that all articles were indexed in MEDLINE, but we did not check this for the whole set. This could have influenced the performance of the search filter. However, the testing of the performance of the filters was done in the last quarter of 2010, and we assume that the majority of articles were indexed by then. In case the search filter would incorrectly not have identified a relevant article because this was not indexed yet, this could only affect the performance negatively.
We split the reference set halfway using the alphabetized list of authors. This could have introduced bias because all the authors with the same first author fall into either the development set or the validation set. However, the percentages of relevant information in both sets are comparable, and therefore we assume the bias is limited.
Because we created the search filters using a reference set that consisted mainly of journals with a high prevalence of geriatric information, we might have overestimated the precision. Still, a slight decrease in the precision when our search filters are applied to MEDLINE is acceptable, because the precision in our test situation was very good.
The quality of any search depends on all components. Therefore, the search for the topic of interest that is combined with our search filter should be methodologically sound. Also, the searcher should determine the methodological quality and appropriateness of the retrieved information before implementing it into daily practice.
Another consideration is the usability and implementation of our best performing searches filters. They consist of multiple search statements and therefore might be complex to use by non-information professionals. For that reason, we want to provide these search filters on open access websites of international geriatric societies. In this way, searchers can easily copy and paste the search filter into MEDLINE (for example into PubMed Filters) and combine it with their topic of interest.

Conclusion

We conclude that our search filters contribute to a more evidence-based treatment for the geriatric patient, because finding relevant literature is the starting point of evidence-based practice. With the filters, searching MEDLINE can readily become more efficient.
Future research should focus on the implementation of these search filters in daily practice and to their contribution to decision making and medical knowledge.

Appendix: the search filters

No. 1: The most sensitive search filter (Se=94.8%, Sp=88.7%)

elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab] OR "mini-mental state" [tiab] OR alzheimer [tiab] OR alzheimer's [tiab] OR alzheimers [tiab] OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR adl [tiab] OR frailty [tiab] OR gds [tiab] OR ageing [tiab] OR "hip fractures " [tiab] OR elders [tiab] OR frail [tiab] OR mci [tiab] OR demented [tiab] OR psychogeriatrics [tiab] OR "cognitive impairment" [tiab] OR "postmenopausal women" [tiab] OR comorbidities [tiab] OR dementia [tiab] OR aging [tiab] OR older [tiab] OR "daily living" [tiab] OR "cognitive decline" [tiab] OR "cognitive impairment" [tiab] OR residents [tiab] OR "cognitive functioning" OR "old people" [tiab] OR nursing homes [mh] OR geriatric assessment [mh] OR aging [mh] OR frail elderly [mh] OR alzheimer disease [mh] OR homes for the aged [mh] OR cognition disorders [mh] OR dementia [mh] OR activities of daily living [mh] OR aged, 80 and over [mh]

No. 2: The most specific search filter (Se=69.1%, Sp=96.6%)

elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab] OR "mini-mental state" [tiab] OR alzheimer [tiab] OR alzheimer's [tiab] OR alzheimers [tiab]OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR adl [tiab] OR frailty [tiab] OR gds [tiab] OR ageing [tiab] OR elders [tiab] OR frail [tiab] OR mci [tiab] OR demented [tiab] OR psychogeriatrics [tiab] OR "cognitive impairment" [tiab] OR "postmenopausal women" [tiab] OR comorbidities [tiab] OR geriatric assessment [mh] OR nursing homes [mh] OR frail elderly [mh] OR cognition disorders/diagnosis [mh] OR cognition disorders/epidemiology [mh] OR homes for the aged [mh] OR alzheimer disease [mh] OR dementia [tiab]

No. 3: Specific search filter with increased sensitivity (Se=75.3%, Sp=96.0%)

elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab] OR "mini-mental state" [tiab] OR alzheimer [tiab] OR alzheimer's [tiab] OR alzheimers [tiab] OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR adl [tiab] OR frailty [tiab] OR gds [tiab] OR ageing [tiab] OR elders [tiab] OR frail [tiab] OR mci [tiab] OR demented [tiab] OR psychogeriatrics [tiab] OR "cognitive impairment" [tiab] OR "postmenopausal women" [tiab] OR comorbidities [tiab] OR geriatric assessment [mh] OR nursing homes [mh] OR frail elderly [mh] OR alzheimer disease/epidemiology [mh] OR cognition disorders/diagnosis [mh] OR cognition disorders/epidemiology [mh] OR homes for the aged [mh]

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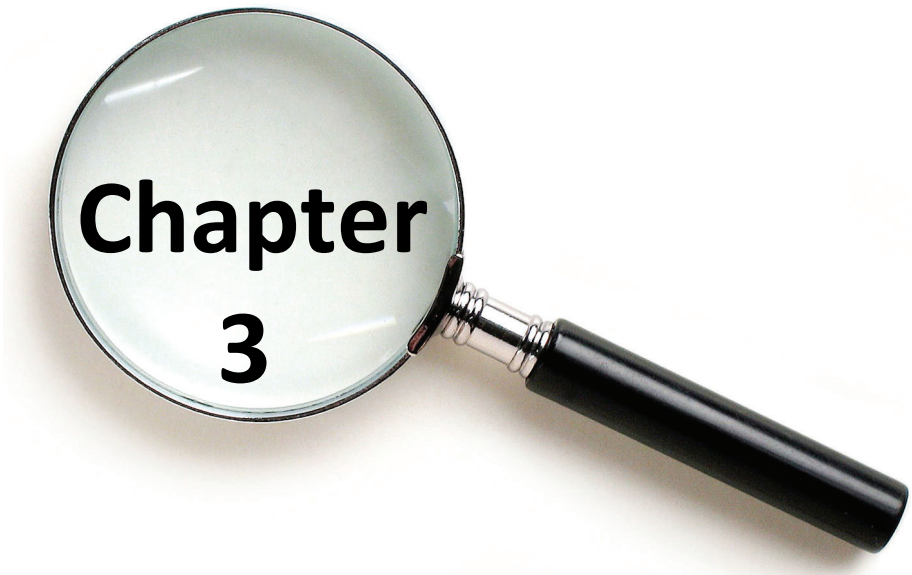

Searching for evidence-based geriatrics: Tips and tools for finding evidence in the medical literature

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Chapter 3

Abstract

Introduction: Information to treat geriatric patients evidence-based is hard to find. Recently, a sensitive and a specific search filter to improve searching for literature relevant to geriatric medicine were developed in a research setting. The aim of this study is to determine whether these filters are able to find the articles considered relevant for daily clinical practice by young geriatricians.

Materials and methods: For this study we included references identified for lectures of the session of the IXth European Academy for Medicine of Ageing (EAMA) course 2011 about 'Ageing and functionality' and lectures of the session entitled 'Evidence-Based Medicine' (EBM). Relevant references were combined with the specific and sensitive search strategy in MEDLINE.

Results: Of the 50 relevant articles for the course 'Functionality', the sensitive filter identified 46 (92%); the specific filter 39 (78%). Of the 92 relevant references on 'EBM', the sensitive filter retrieved 80 (87%), the specific filter 59 (64%). Articles not identified by the sensitive filter were mostly missed because the filter specifically searched for relevant terms mentioned in title or abstract.

Conclusion: Geriatricians can be confident that the majority of relevant articles will be retrieved by the sensitive search filter. Searching for literature will be simplified and made more efficient by using a search filter. By demonstrating the pros of the filter we hope to stimulate implementation in daily clinical practice, so our elderly population is as much treated by the most up to date available evidence as possible.

Introduction

The ageing population poses an increasing demand on health professionals. Geriatric patients often have multiple chronic conditions, resulting in the use of several medications. A study about prevalence of morbidities in the elderly showed that 82% of patients aged 65 and over had at least one chronic condition; 24% had even four or more conditions (1). Due to deteriorating organ functions they are prone to medication-related side effects (2). Consequently, the care for elderly is complicated. To provide the best care, doctors need to base their decision on valid evidence.

However, evidence specifically directed to geriatric patients is hard to find for several reasons. Geriatric medicine overlaps with, among others, psychiatry, internal medicine and neurology and therefore, evidence on geriatrics is published in a wide range of journals. In addition to that, the amount of available information is increasing rapidly, and time for searching is limited. Even though bibliographic databases often provide tools to simplify searching (e.g. Medical Subject Heading (MeSH) terms in MEDLINE), correctly using these tools is challenging. Moreover, indexing for MEDLINE is not always consistent; furthermore it lags months behind so that recently published articles will not be found when only MeSH-terms are used. In sum, finding the best and most up to date evidence can be challenging, especially for a busy clinician. However, general tools to help finding evidence-based literature relevant for a specific clinical subject in medicine are currently more wide spread (3). Previously, researchers have developed search filters for different purposes (4;5). Search filters consist of MeSH terms and text words in titles and abstracts that are related to the subject of the intended search.

Van de Glind et al developed a search strategy or 'filter' to find the answers to clinical questions concerning geriatric patients more efficiently than with a general search in the whole database (Table 1) (6).

Table 1: Specific and sensitive filter

Specific filter	Sensitive filter
elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab OR "mini-mental state" [tiab] OR alzheimer [tiab] OR alzheimer's [tiab] OR alzheimers [tiab] OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR Adl [tiab] OR frailty [tiab] OR gds [tiab] OR ageing [tiab] OR elders [tiab] OR frail [tiab] OR mci [tiab] OR demented [tiab] OR psychogeriatrics [tiab] OR "cognitive impairment" [tiab] OR "postmenopausal women" [tiab] OR Comorbidities [tiab] OR geriatric assessment [mh] OR nursing homes [mh OR frail elderly [mh] OR cognition disorders/diagnosis [mh] OR cognition disorders/epidemiology [mh] OR homes for the aged [mh] OR alzheimer disease [mh] OR dementia [tiab]	elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab] OR "mini-mental state" [tiab] OR alzheimer [tiab] OR alzheimer's [tiab] OR alzheimers [tiab] OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR adl [tiab] OR frailty [tiab] OR gds [tiab] OR ageing [tiab] OR "hip fractures " [tiab] OR elders [tiab] OR frail [tiab] OR mci [tiab] OR demented [tiab] OR psychogeriatrics [tiab] OR "cognitive impairment" [tiab] OR "postmenopausal women" [tiab] OR comorbidities [tiab] OR dementia [tiab] OR aging [tiab] OR older [tiab] OR "daily living" [tiab] OR "cognitive decline" [tiab] OR "cognitive impairment" [tiab] OR residents [tiab] OR "cognitive functioning" OR "old people" [tiab] OR nursing homes [mh] OR Geriatric assessment [mh] OR aging [mh] OR frail elderly [mh] OR alzheimer disease [mh] OR homes for the aged [mh] OR cognition disorders [mh]OR dementia [mh] OR activities of daily living [mh] OR aged, 80 and over [mh]

Searchers could, for example, combine 'heart failure' with this geriatric search strategy to retrieve mainly articles relevant for the geriatric patient with this disease. The most sensitive search strategy had a sensitivity of 92.0%, a specificity of 86.9%, and a number needed to read (NNR) of 1.40. The most specific search strategy had a specificity of 96.0%, a sensitivity of 69.6%, and a NNR of 1.16. With regard to search filters, sensitivity is regarded as the proportion of relevant studies detected in the literature and specificity as the proportion of irrelevant studies that are excluded by the search. The NNR indicates how many articles have to be screened in order to find one relevant article. These geriatric search strategies could simplify searching for relevant literature by lowering the number of articles needed to read to find a relevant study and therefore, attribute to a better evidence-based practice. The search strategies are not only useful to the clinician who wishes a quick answer to a clinical question, but also to the researcher who wants to find as many articles as possible without missing too much relevant information, for example for systematic reviews or guideline development. Moreover, when searching in MEDLINE, extra studies that are not indexed with MeSH terms, can be identified.
However, although the search filter was tested and validated in a research setting, the usability in daily clinical practice is unknown. Additionally, the unknown possibility to miss relevant articles by using the filters could theoretically limit the implementation. Therefore the aim of this study is to determine whether the various geriatric search filters are able find the articles considered relevant in daily clinical practice by young geriatricians.

Methods

For this study we used articles considered relevant in daily clinical practice by young geriatricians for lectures of the IXth European Academy for Medicine of Ageing (EAMA) course 2011 as a validation set. The hypothesis is that our search filters do not miss the references used by the EAMA students.
The EAMA is an Advanced Postgraduate Course in Geriatrics since 1995. The two-year course consists of four one-week sessions held twice a year. Each session covers a well-balanced geriatric topic with experts from around the world. This course is directed towards faculty members of departments of geriatrics, academic teachers planning a career in geriatrics or in medical gerontology. The course can also be attended by junior potential academic staff working in other fields (internal medicine, sub-specialties, biology) involving the ageing process and care of elderly people. The program aims to increase scientific, clinical, educational and managerial competences in medical gerontology. Students have to prepare a state of the art lecture about a specific appointed relevant subject for geriatric medicine. For this lecture they have to search evidence-based and choose maximal five relevant references.
The validation set for this study consists of articles found by the 16 students of the first session of the IXth EAMA course 2011 about 'Ageing and functionality' and the 25 students of the second session entitled 'Evidence-Based Medicine'. References for the

lectures were searched by students with little to average experience in searching electronic databases without making use of the geriatric search filters. Searches were not limited to a specific database, but were predominantly performed in MEDLINE. All study types, including guidelines, were allowed.

Because our search filters were developed for MEDLINE, we first checked the presence of the references found by the students in MEDLINE. References not available in MEDLINE were excluded. Two reviewers (BM and EG) independently reassessed the relevance for geriatrics of the available records. Articles were categorized as relevant for geriatric medicine if they described a condition of old age. Also, studies that included patients with mean age above 70, or that did a subgroup analysis in patients aged 70 years or above were considered relevant for geriatrics. These criteria are in agreement with the ones we used at the development of the search filters (6).

The relevant references were in two independent search strategies combined with the Boolean operator AND to firstly the specific and secondly the sensitive search strategy in MEDLINE (PubMed). The proportion of false negative results of these two strategies (missed relevant papers) was calculated to give an impression of the sensitivity of the filters for daily clinical practice.

Results

Of the 72 used articles for the EAMA course 'Functionality', 61 (85%) could be retrieved in MEDLINE. In total, 50 records (82% of 61) were considered relevant for geriatric medicine. The sensitive search filter found 46 (92%) of these records (Table 2).

Table 2: Overview of identified articles

Subject Lecture EAMA	Functionality	Evidence-Based Medicine
Articles in MEDLINE	61	112
Articles considered relevant (%)	50 (82)	92 (82)
Relevant articles identified with sensitive filter (%)	46 (92)	80 (87)
Relevant articles identified with specific filter (%)	39 (78)	59 (64)

The specific search filter retrieved 39 of the relevant articles (78%). In the course on 'EBM', 121 references were identified. Four references were excluded because they were duplicates, five5 were not available in MEDLINE, and 30 were considered irrelevant. Of the 92 (82%) remaining relevant articles, the sensitive filter retrieved 80 (87%) and the specific filter 59 (64%). The articles considered irrelevant of both courses were on general not geriatric topics or comprised for example guidelines without subgroup description of elderly.

Because it is most essential to feel confident specifically about the sensitive filter not too miss important articles, we determined the nature of the missed articles by this filter. Considering the EAMA course on 'Functionality', the sensitive filter missed four studies that were considered relevant to geriatrics (Table 3).

Table 3: Reasons for not identifying the article relevant for geriatrics by the sensitive filter

Reason	Number of articles - functionality (n=4)	Number of articles - Evidence-Based Medicine (n=12)
Guidelines on general topics	0	3
Systematic reviews on general topics	4	3
Experts opinions on general topics	0	2
Narrative review	0	1
Primary research	0	3

These concerned three reviews about osteoarthritis and one systematic review about artificial nutrition (7-9). These studies include a relevant paragraph considering treatment of elderly patients, but do not mention this in the abstract. This explains why these articles were not identified by the sensitive filter, because our filters only search for terms mentioned in title or abstract. From the references of the course on evidence-based medicine, the sensitive filter missed 12 relevant studies. Of these, three were guidelines (10-12) and two were expert opinions (13;14). Two were systematic reviews about diseases that are prevalent at older age (15;16), one was a narrative review (17). The other three were primary research on general conditions that included elderly patients as well (18-20).

Discussion

This research showed that both the sensitive and specific geriatric search filters were able to find respectively 92%/87% and 78%/64% of the articles considered relevant for daily clinical practice by young geriatricians from all over Europe. This means that physicians involved in elderly care can be confident that the majority of relevant articles for daily practice will be retrieved by using the filter in their literature searches.

Because we were not able to investigate the individual search strategies prospectively, we could not calculate the number needed to read in daily clinical practice. Based on our findings we can only assume that using the search filter will save time in daily clinical practice, by a lower NNR of the abstracts. Also it is unknown if the students missed some relevant articles; possibly the yield might have been even higher in case the search filter would have been used. Especially, the most recent studies might only have been identified by using the filters, as indexing by databases lags behind and is not always consequent. Moreover, it was shown before that in searches performed with search filters the number of relevant articles is higher than than in searches done without filter (4).

The filter performed better in retrieving the references from the lectures about functionality. Most probably this is related to the fact that articles describing functional problems often include older patients and by that are relevant for geriatric medicine. On the other hand, articles considering evidence based medicine concern a more general topic and are often not directed to our elderly population. Because the filters use terms mentioned in title or abstract, it will miss articles that have a subparagraph about treatment of the elderly, for example in a large guideline. Probably, the search filters are

more usable to find primary studies than aggregated evidence, because most guidelines do not mention older people in the abstract but only in subparagraphs. As we expected, the fraction of identified articles of the specific filter is lower than the fraction of the sensitive filter with the advantage of a lower NNR. Which search strategy is best to use depends on the aim of the search. If the searcher needs to be sure that few relevant articles are missed, the sensitive filter is suitable. If the searcher needs a quick answer on a clinical question, it is better not to screen many irrelevant results. Then the specific filter is best to use.

By demonstrating the pros of the filter we hope to stimulate implementation in daily clinical practice, so that our elderly population is as much treated by the available evidence as possible. Moreover we hope that by simplifying searching for literature, the shortage of studies in this target group becomes even more burdensome and will stimulate both researchers and grant suppliers to fill this gap.

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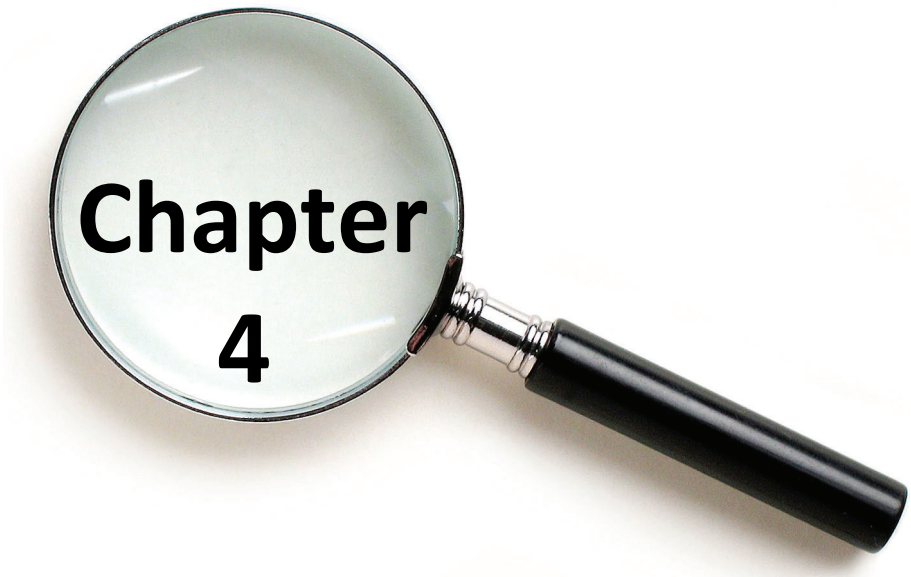

Pre-arrest predictors of survival after resuscitation from out-of-hospital cardiac arrest in the elderly – a systematic review

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Abstract

Introduction: To enable older people to make decisions about the appropriateness of cardiopulmonary resuscitation (CPR), information is needed about the predictive value of pre-arrest factors such as comorbidity, functional and cognitive status on survival and quality of life of survivors. We systematically reviewed the literature to identify pre-arrest predictors for survival, quality of life and functional outcomes after out-of-hospital (OHC) CPR in the elderly.

Methods: We searched MEDLINE (through May 2011) and included studies that described adults aged 70 years and over needing CPR after OHC cardiac arrest. Prognostic factors associated with survival to discharge and quality of life of survivors were extracted. Two authors independently appraised the quality of each of the included studies. When possible a meta-analysis of odd's ratios was performed.

Results: Twenty-three studies were included (n=44,582). There was substantial clinical and statistical heterogeneity and reporting was often inadequate. The pooled survival to discharge in patients >70 years was 4.1% (95% CI 3.0-5.6%). Several studies showed that increasing age was significantly associated with worse survival, but the predictive value of comorbidity was investigated in only one study. In another study, nursing home residency was independently associated with decreased chances of survival. Only a few small studies showed that age is negatively associated with a good quality of life of survivors. We were unable to perform a meta-analysis of possible predictors due to a wide variety in reporting and statistical methods.

Conclusions: Although older patients have a lower chance of survival after CPR in univariate analysis (i.e. 4.1%), older age alone does not seem to be a good criterion for denying patients CPR. Evidence for the predictive value of comorbidities and for the predictive value of age on quality of life of survivors is scarce. Future studies should use uniform methods for reporting data and pre-arrest factors to increase the available evidence about pre arrest factors on the chance of survival. Furthermore, patient-specific outcomes such as quality of life and post-arrest cognitive function should be investigated too.

Introduction

Cardiopulmonary resuscitation (CPR), which was developed in the 1950s (1), is a treatment for cardiac arrest, which is a potentially lethal condition. Unfortunately, the success rates for CPR are poor. The percentage of patients who leave the hospital alive following the procedure varies from 0% to 20% and has not significantly improved in the last 30 years (2;3). This might be caused by the increasing age of the population, longer EMS response time intervals attributable to urbanization and population growth and the declining incidence of ventricular fibrillation arrests (3).

With increasing age, the prevalence of morbidity and disability clearly increases, while perceived health status and physical well-being decrease (4-6). The question arises whether CPR is appropriate for elderly patients who are multiply impaired and have limited life expectancy given their reduced likelihood of survival with a reasonable quality of life.

Many studies and reviews have reported on the chances of success. Sasson et al. studied the survival of out-of-hospital cardiopulmonary resuscitation and found that the success rate depends on arrest factors, such as witnessed arrest, provision of bystander CPR, shockable cardiac rhythm, time to arrival of ambulance and recovery of spontaneous circulation (ROSC) before hospital admission (3). However, all or most of these factors are unknown when the decision about CPR is made. A recent meta-analysis by Ebell et al.(2) identified several pre-arrest predictors of failure to survive cardiopulmonary resuscitation for the in-hospital setting, although these factors were investigated in only few studies.

In spite of the wealth of literature, the exact effects of age and pre-arrest factors on survival remain unclear. Furthermore, it is unclear whether failure to survive in an out-of-hospital setting depends on age alone or on other pre-arrest factors such as cognitive impairment and comorbidity that are more prevalent at older ages (7;8).

In this systematic review, we aim to provide an overview of the current evidence on the association between pre-arrest factors and the probability of survival to discharge and beyond after out-of-hospital cardiac arrest (OHCA) and the quality of life of elderly (>70 years) survivors. This could inform the decision-making process about the desirability of cardiopulmonary resuscitation with evidence on the actual chances of survival in good health in patients with advanced age, comorbidity and/or nursing home residency.

Methods

Search strategy

We searched MEDLINE with an extensive search strategy to identify studies published between January 1980 and May 2011 that investigated prognostic factors for survival of out-of-hospital CPR. In addition, we checked the reference lists of the selected studies to identify missing relevant articles and we used a multidisciplinary Dutch guideline about decision-making on resuscitation in older patients as an additional source of studies (9). For this guideline, MEDLINE, Embase, Web of Science, CINAHL, Cochrane DSR, DARE and

Cochrane Controlled Trial Register and DARE were searched to identify studies published between 1950 and 2008.
The root search was a combination of synonyms for cardiopulmonary resuscitation ([cardiopulmonary resuscitation OR [CPR OR [mouth to mouth) and search terms for cardiopulmonary arrest ([heart arrest OR [cardiac arrest OR [cardiopulmonary arrest OR [sudden death) combined with outcomes ([quality of life OR "cerebral recovery"[tiab OR [functional impairment OR "hospital discharge"[tiab). All search terms were entered as free text words and as Medical SubHeadings (MeSH-terms). To limit the results to the geriatric population, we used a sensitive filter for geriatric medicine (10). The search strategy is available through the authors.

Study selection
First, one author (EvdG) selected studies based on the titles and abstracts. Then, two researchers (EvdG and FvdW) screened the full texts of the remaining articles more thoroughly. Disagreements were discussed with a third reviewer (LH). Only studies that were written in English were included.
For this review, we included studies that investigated patients who required CPR for a cardiopulmonary arrest in an out-of-hospital setting (including nursing homes). We defined cardiopulmonary arrest as the sudden cessation of spontaneous circulation and respiration leading to loss of consciousness and death when CPR is not provided. CPR was defined as the use of chest compressions and rescue breathing, with or without advanced life support, delivered according to the protocols that were applied in the study period.
We included studies in which the mean age of the participants was 70 years or more or in which different age groups were presented separately, including patients aged 70 years or more. Eligible studies assessed ‘age’ as a clinical predictor of survival or mortality after CPR, or as predictor for the quality of life of survivors, both univariably and multivariably. Studies also had to report ‘survival to discharge’ as a main outcome measure; studies that only reported ‘recovery of spontaneous circulation (ROSC)’ or ‘hospital admission’ were excluded. We excluded studies that described patients with loss of consciousness due to seizure, sole respiratory arrest or cardiopulmonary arrest due to trauma or drowning.

Quality assessment
To assess the methodological quality of the included studies, we used a checklist based on the checklist developed by Hayden et al.(11) This checklist assesses six domains of bias in a systematic review of prognosis studies (Table 1). Each item could score ‘low risk of bias’, ‘moderate risk of bias’, ‘high risk of bias’ or ‘unknown risk of bias’.
Two researchers (EvdG and FvdW) independently performed the quality assessment. When necessary, disagreements were resolved through discussion with a third reviewer (LH).

Table 1: Quality assessment of included studies

Potential Bias	Items to be considered for assessment of potential bias:
Study participation	Low risk of bias was assessed if no patients group was excluded from the study cohort and when in- and exclusion criteria were adequately described. Moderate risk of bias was assessed if the sample was not adequately described for key characteristics (age, sex, arrest characteristics). High risk of bias was assessed when both items were not adequately addressed.
Study attrition	Low risk of bias was assessed if there was no difference between eligible patients registered in a database and the number being analyzed. Also, there should have been no important differences between key characteristics and outcomes in participants who were analyzed the study and those who were not. Moderate risk of bias was assessed if loss to follow-up was described but was less than 20%. High risk of bias was assessed when loss to follow-up was not described or was >20% .
Prognostic factor measurement	Moderate risk of bias was assessed if at least the prognostic factor 'age' was taken into account. Low risk of bias was assessed when comorbidity and either functional dependence or comorbidity were reported. The prognostic factor measure and method should have been adequately valid and reliable to limit misclassification bias. The method and setting of measurement should have been the same for all study participants. When this was not the case, the risk of bias was assessed one step higher.
Outcome measurement	For the outcome 'survival', this item was not applicable. The outcomes 'quality of life' and 'functional status' of survivors were assessed separately. These outcomes should have been measured using a reliable and adequately valid method, in order to assess a low risk of bias.
Confounding measurement and account	Low risk of bias was assessed when was adjusted for all relevant confounders (shockable rhythm, witnessed arrest, provision of bystander CPR, interval to bystander or EMS CPR start). If was adjusted for only one or two factors, the risk of bias was assessed as moderately. Measurement of confounders should have been adequately valid and reliable, and method and setting of confounding measurement should be the same for all study participants. High risk of bias was assessed when no adjustment for confounders had taken place.
Analysis	Low risk of bias was assessed when there was sufficient presentation of data to assess the adequacy of the analysis. When only the significant factors were reported in the multivariate analyses, or when adjustment factors were not reported, the risk of bias was assessed higher.

Data extraction

We used a standardized form to collect information on patients' demographic and arrest characteristics. Furthermore, we extracted data on survival to discharge and beyond and on the quality of life, cognitive and functional status of survivors if reported. The reported arrest characteristics are all known to influence the outcome of cardiopulmonary resuscitation and can be considered as confounders for which analyses should be adjusted (3;12).

The outcomes 'survival to discharge' and '30-day survival' were combined into short-term survival. Other outcome measures, such as long-term survival, quality of life and functional dependence of survivors, were reported separately.

Analysis

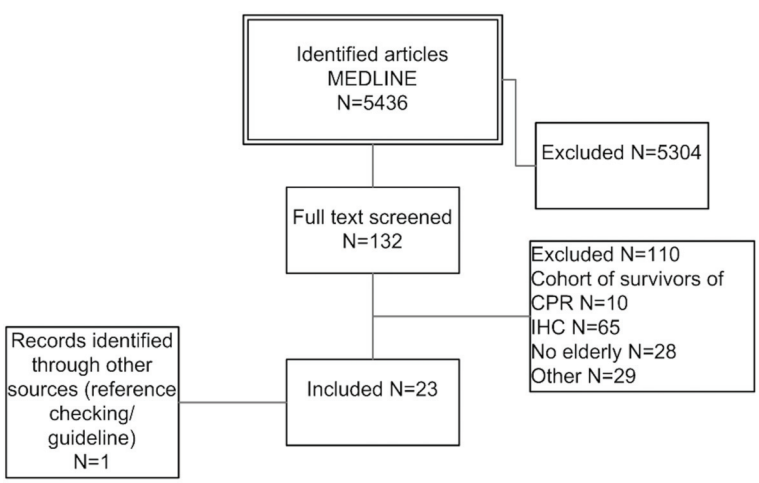
For studies that exclusively included participants aged 70 years or above or reported data on a subgroup with this age and were sufficiently similar with respect to the participant and arrest factors, we calculated a pooled overall survival rate. We used an exact likelihood approach based on the binomial within-study distribution. This model allows for zero survivors in one or more studies (13). Because we expected substantial heterogeneity in the reporting of quality of life and functional dependence, we did not pool these results. Nor did we perform a meta-analysis of the prognostic accuracy of the various individual prognostic factors, since we expected substantial heterogeneity between the primary studies, for example in the number and type of covariates that were studied and, more importantly, in the predictors that were included in a multivariable adjusted analyses (if done)(14;15).

Results

Identification of studies

The search resulted in 5,436 articles (Figure 1). Of the 132 potentially relevant articles, 22 were included. The main reasons for exclusion were a mean age below 70 or no separate subgroup with participants >70 years and the examination of in-hospital CPR only. From the large Swedish cohort study by Herlitz, from which many reports were published, we included one key publication that met the inclusion criteria (16).

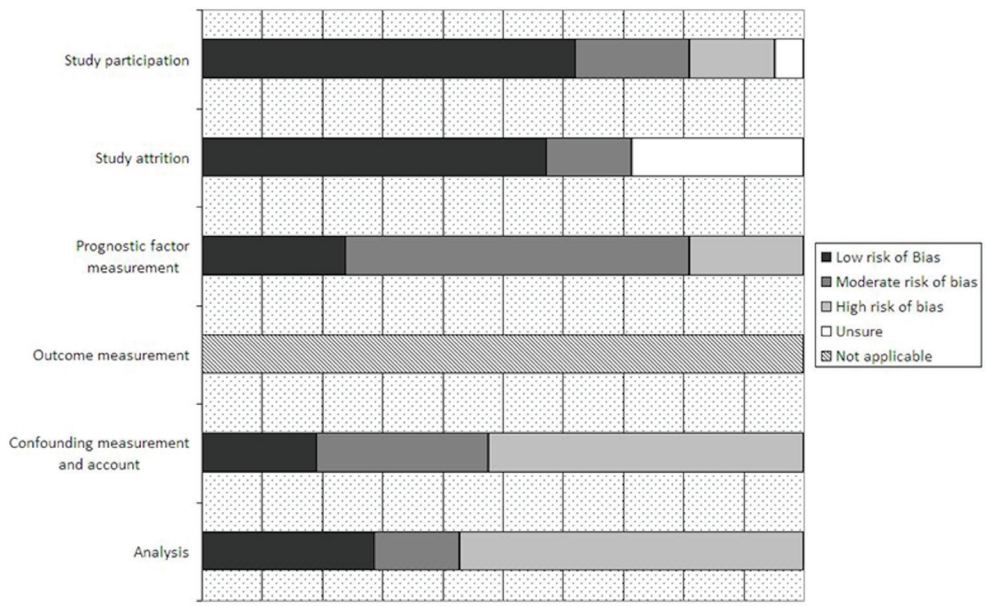
Figure 1: Flowchart of selection of studies. IHC= in hospital cardiac arrest



Quality assessment

The majority of the studies scored a low-to-moderate risk of bias on the items of study participation, study attrition and prognostic factor measurement (Figure 2).

Figure 2: Quality assessment of included studies



When a high risk of bias was assessed for the domain of study participation, it was because important baseline characteristics such as comorbidity or age were missing. In addition, some studies addressed a specific patient group that did not match the current research question. For example, some studies only described witnessed arrests or only included patients who were admitted alive (17;18). The reasons for not reporting on the entire cohort of resuscitated patients in the analysis were not always listed. Therefore, it was not clear whether there were differences between the participants who were analyzed and those who were not, which could have introduced bias on the item of study attrition.

On the item of prognostic factor measurement, most of the studies were assessed as having a moderate risk of bias. Typically, the prognostic factor 'age' was described; however, other factors, such as co-morbidity or functional dependence, were often not reported. In these cases, the score on this domain was 'moderate risk of bias' at best.

In all cases the outcomes quality of life and functional and cognitive status of survivors were measured adequately and reliable, and therefore we assessed no risk on misclassification bias on this item.

In only a few cases, the items of confounding and analysis could be assessed as low risk of bias, because adjustment for response time, percentage bystander CPR and type of

rhythm was generally poorly controlled. Furthermore, when a multivariate analysis was performed, only the variables that were statistically significantly associated with the outcome in the univariate analysis were typically presented, explaining the low score on the 'analysis' item.

Characteristics of the included studies

Table 2 (appendix) shows the characteristics of the 23 included studies. The total number of included patients was 44,582, with an age range of 33-99 years. Of the studies, four exclusively included elderly patients (17;19-21). In five of the studies, the mean age of the included patients was 70 years or above (22-26). Fourteen studies provided a subgroup of elderly patients. For these studies, only the proportion survival in the oldest group is presented in table 2 (16;18;27-38).

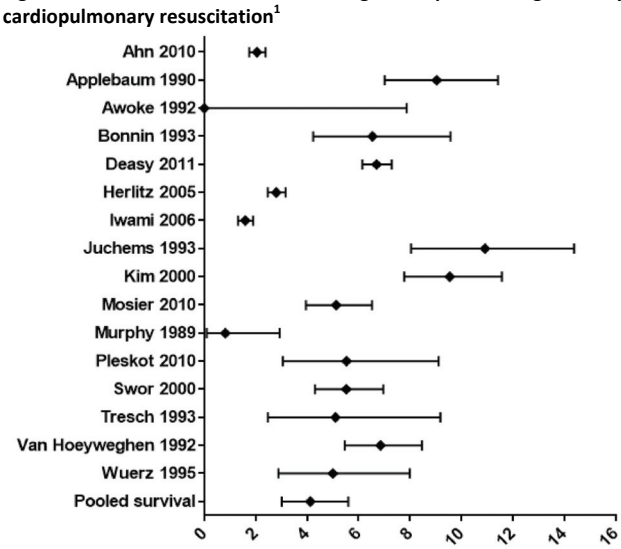
Thirteen studies were performed in the USA, and eight in Europe. The study populations and registered pre-arrest characteristics varied across studies. All studies were retrospective cohort studies or chart reviews, with the exception of Ghusn (17), which was a case control study. All but one study (38) reported at least survival to discharge; seven reported long term outcomes as well (23;25;27;36-38).

Findings of the included studies

Survival

Fourteen studies were sufficiently clinically homogeneous to perform a meta-analysis for survival (Figure 3).

Figure 3: Pooled survival to discharge for patients aged 70 years and over after out of hospital cardiopulmonary resuscitation[1]



[1] This figure is a corrected version from the one that was published in the BMC geriatrics

Table 3a: Reported Odd's Ratio's (OR) of included studies for survival after CPR

	Prognostic factor	Crude ORs (95% CI)	OR in multivariate analysis (95% CI)	Factors included in multivariate analysis
Applebaum 1990 (19)	Nursing home residency	0.14 (0.04-0.61)	NR	Not applicable
Ahn 2010 (22)	Age 15-64 y Age ≥ 65 y Gender (male)	1.0 0.54 (0.44-0.65) 1.57 (1.29-1.92)	1.0 0.50 (0.41-0.62) 1.14 (0.93-1.42)	Gender, age, location, witness, initial rhythm, elapsed time interval before start BLS and ALS, level of EMS provider (basic or intermediate).
Deasy 2011 (29) (Non-shockable rhythms)	Age 65-69 y Age 70-74 y Age 75-59 y Age 80-84 y Age 85-89 y Age 90-94 y Age 95-99 y	1.0 0.87 (0.69-1.09) 0.84 (0.68-1.05) 0.78 (0.62-0.97) 0.61 (0.48-0.79) 0.42 (0.30-0.60) 0.20 (0.08-0.50)	1.0 0.93 (0.73-1.19) 0.88 (0.69-1.11) 0.86 (0.67-1.09) 0.65 (0.49-0.85) 0.45 (0.31-0.65) 0.21 (0.08-0.52)	Witnessed arrest, year in which arrest took place, sex, provision of bystander CPR, EMS response time, location of arrest.
Deasy 2011 (29) (Shockable rhythms)	Age 65-69 y Age 70-74 y Age 75-59 y Age 80-84 y Age 85-89 y Age 90-94 y Age 95-99 y	1.0 1.17 (0.92-1.49) 1.24 (0.98-1.58) 0.92 (0.71-1.19) 0.85 (0.62-1.18) 0.75 (0.45-1.25) 0.12 (0.01-0.93)	1.0 1.25 (0.97-1.61) 1.29 (1.00-1.65) 0.87 (0.66-1.15) 0.82 (0.59-1.15) 0.72 (0.42-1.24) 0.11 (0.01-0.87)	Witnessed arrest, year in which arrest took place, sex, provision of bystander CPR, EMS response time, location of arrest.
Fabbri 2006 (37)	Age >74 y vs. <74 Gender (male) Heart failure Cardiovascular disorder Hypertension Diabetes mellitus	0.39 (0.21-0.71) 2.21 (1.11-4.41) 0.04 (0.03-0.31) 0.28 (0.11-0.72) 0.38 (0.17-0.86) 0.36 (0.16-0.82)	0.41 (0.87-0.93) 3.5 (1.18-10.36) 0.37 (0.14-0.99) 0.40 (0.16-1.00) 0.34 (0.14-0.83) 0.70 (0.58-0.85)	Initial rhythm, sex, age, comorbidity (history of diabetes, hypertension, myocardial infarction), seasonality, day-week, day-times, urban setting, home location, response times.
Herlitz 2005 (16)	Age > 73 y vs. < 73 y Gender (male)	0.53 (0.46-0.62) 1.14 (0.97-1.33)	0.63 (0.50-0.71) NR	Witnessed arrest, initial rhythm, provision of bystander CPR, ALS response interval, age, sex.
Iwami 2006 (38)	Nursing home	0.96 (0.39-2.4)	NR	
Kim 2000 (31)	Age (per decade) Gender (male)	NR NR	0.92 (0.85-0.99) 1.03 (1.32-0.77)	Witnessed arrest, initial rhythm, sex, age, provision of bystander CPR, location of arrest
Mosier 2010 (32)	Age (per decade)	NR	0.79 (0.67-0.93)	Witnessed arrest, VF, agonal respirations, EMS response time, age.
Swor 2000 (33)	Age 50-59 y Age 60-69 y Age>70-79 y Age > 80 y	1.0 0.81 (0.52-1.26) 0.70 (0.44-1.10) 0.31 (0.17-0.57)	1.0 0.86 (0.52-1.42) 0.83 (0.50-1.37) 0.40 (0.20-0.82)	Witnessed arrest, VF, provision of bystander CPR, ALS response interval <9 min.

For patients aged 70 years or older, the pooled overall survival to discharge was 4.1% (95% confidence interval (CI) 3.0-5.6%; range 0-9.0%) (Table 3). This was lower than the general survival, as reported by Sasson et al. (pooled survival 7.6% (95% CI 6.7-8.4%) (3).
There was substantial clinical and statistical heterogeneity and reporting of statistical methods was often inadequate. Performing a meta-analysis of odd ratio's (ORs) was impossible due to a wide variety in the statistical methods used such as the adjustment factors and the statistical models. Table 3 shows that the chance of survival significantly decreased as age increased, both in univariate (16;22;29;31-33;37;38) and multivariate analyses (16;22;29;31-33;37). In the multivariate analyses, most studies included only

arrest factors, such as 'witnessed arrest', 'bystander arrest' and 'shockable rhythm' in the model; thus, these studies do not clarify the influence of pre-arrest comorbidity and functional status. Only the study of Fabbri (37) analyzed the effect of pre-arrest co-morbidities on the chance of survival (see Table 3). However, this study did not adjust for arrest factors and only examined witnessed arrests. Of the 23 included studies, six studies investigated the predictive value of nursing home residency for decreased survival to discharge (17;19;20;29;31;38) (Table 3b). For this group, the absolute survival chances were low and ranged from 0-5.1%. One study showed that nursing home residency was significantly associated with a lower chance of survival to discharge (OR 0.14)(19), whereas Deasy et al. presented a significant OR of 0.26 that was adjusted for arrest factors (29). Although there were limited studies these data show that the chance of survival for this group is lower.

Table 3b: Reported Odd's Ratio's (OR) for nursing home residence of included studies for survival after CPR

	Prognostic factor	**Crude ORs (95% CI)**	**OR in multivariate analysis (95% CI)**	**Factors included in multivariate analysis**	**Outcome**
Iwami 2006 (38)	Nursing home (witnessed cases) vs. arrest in other place	0.96 (0.39-2.4)	NR	Not applicable	1 year survival
Applebaum 1990 (19)	Nursing home residents vs. matched cohort	0.14 (0.04-0.61)	NR	Not applicable	Surivival to discharge
Kim 2000 (31)	Arrest in nursing home	NR	0.61 (0.31-1.20)	Witnessed arrest, initial rhythm, sex, age, provision of bystander CPR, location of arrest	Survival to discharge
Awoke 1992 (20)	No comparison made: "no resident survived to discharge from the hospital"				Survival to discharge
Deasy 2011 (29)	Nursing home residency vs. arrest at home/public place/ other (non shockable rhythms)	NR	0.26 (0.11-0.60)	Witnessed arrest, year in which arrest took place, sex, provision of bystander CPR, EMS response time, location of arrest.	Survival to hospital discharge
Ghusn 1995 (17)	Patients admitted alive: Nursing home residents vs. matched cohort of older community residing persons	1.15 (0.55-2.45)	NR		Survival to discharge

Quality of life, functional and cognitive status of survivors

Of the included studies, eleven reported on characteristics of survivors such as functional and cognitive status(18;21;23;27;28;31;32;36-38) (Table 2). Quality of life of survivors was reported in only one study(25).

Two studies reported that 7.5% of the patients for whom resuscitation was attempted survived neurologically intact to one year; however, one of these studies only examined witnessed arrests (37), and the other did not specify this outcome for older patients (23). In patients that did not regain and sustain vital signs in the field, only 0.6% survived to discharge neurologically intact (24). Other studies that included only patients over 70 years showed that although the overall survival was low, the majority of the survivors displayed moderate to good cerebral performance (18;25;27;31;36). The study of Pleskot et al. showed no difference between younger and older survivors in cerebral performance, but the number of survivors was insufficient to identify significant differences (27).

In the Horsted study, survivors rated two of the eight quality of life aspects of the SF-36 scale as significantly worse than the age-matched normative scores. However, no specification for age was made (25).

Discussion

Our review showed that, in general, patients aged over 70 years had less chance of surviving to discharge after an out-of-hospital cardiac arrest (4.1% (95% CI 3.0-5.6%)) than the patients of all age groups reported in a previous review (pooled survival 7.6% (95% CI 6.7-8.4%) (3). Furthermore, the factors of nursing home residency (19;20;29;31;38) and pre-arrest comorbidity (37) were associated with decreased chances of survival. It was striking that only one study investigated the predictive value of pre-arrest comorbidity (37). Although the studies that reported on cognition, functional performance and quality of life of survivors were heterogeneous and not specifically concerned older people, the conclusion can be drawn that most of the survivors were in acceptable health.

Information on the quality of life of survivors was scarce in the included studies. In the literature, there are some other studies available that investigated the quality of life of a group of survivors. Two studies showed, that in all age groups, post-resuscitation patients rated their quality of life significantly lower than that of the general population (25;39), whereas others showed that survivors rated their quality of life the same as a matched cohort (31;40). In one study, age above 80 years was independently negatively associated with a good quality of life compared to age- and sex-matched samples from a cohort study (OR 0.3 (95% CI 0.1-0.8) (41). Whether this lower quality of life would be a justification for a do-not-resuscitate order is hard to define and is dependent on patient's preferences. Furthermore, because of the conflicting results, larger cohort studies are necessary to define the true effect of resuscitation on quality of life in post-resuscitation patients.

Although the available evidence on the effect of pre-arrest factors on survival is limited, it is important to accurately inform older people of their limited chances of survival following out-of-hospital CPR. Adams et al. showed that elderly patients' beliefs regarding

the chances of survival after CPR are overly optimistic. Similarly, physicians' expectations of the likelihood of survival are not realistic (42). However, older people understand prognostic information, and such information may alter their preferences with respect to resuscitation (43). Decisions about CPR require the shared decision making of the physician and patient (or proxy). This kind of treatment decisions should be based on both scientific evidence and doctor's and patient's preferences.

Our review has several limitations most of which are related to the retrospective design and quality of the original studies (44). Firstly, there was large heterogeneity in reported outcomes, variables and patient groups. Secondly, many studies did not report the number of cases for which CPR was not attempted. We assumed that this group was in poorer health than the group that experienced a CPR-attempt, thereby overestimating the chances of survival of the entire group. Notably, in the study by Deasy et al., the percentage of patients for whom resuscitation was not attempted increased with age (29). Third, the reported survival percentages varied, which may be partially explained by the varied CPR protocols and access to emergency services across the studied cohorts. Furthermore, most authors only reported the factors that were significantly associated with survival, which resulted in a high risk of bias on this item.

Ebell et al. proposed guidelines for future research on survival after in-hospital CPR. We believe that most of these recommendations are valid for out-of-hospital CPR too (44). Their most important recommendation is uniform reporting of predictor variables, in- and exclusion criteria, demographic data and definitions of cardiopulmonary arrest and resuscitation.

Although our aim was to provide older patients and their doctors with sufficient information about the chances of older people to survive resuscitation in good health, the available evidence appeared to be limited. From our data, it is not clear if age per se is a limiting factor, because most studies did not adjust for pre-arrest factors. Moreover, there was considerable statistical and clinical heterogeneity, because of which performing a meta-analysis of ORs was impossible.

Cohort studies of the predictors of survival of CPR with consistent reporting of the statistical methods and results of studies would facilitate the undertaking of meta-analysis. This would provide useful information for prognostication for elderly (14). As quality of life and cognitive and functional status are even more important at older age than survival per se, these outcomes should be reported too in future studies. This would help both doctors and patients in decision-making about the desirability of cardiopulmonary resuscitation.

Conclusion

Although older patients have a lower chance of survival after CPR in univariate analysis (i.e. 4.1%), older age alone does not seem to be a good criterion for denying patients CPR. Evidence for the predictive value of comorbidities and for the predictive value of age on quality of life of survivors is scarce. Nursing home residency (19;20;29;31;38) and pre-

arrest comorbidity (37) were associated with decreased chances of survival. Future studies should use uniform methods for reporting data and pre-arrest factors to increase the available evidence about pre arrest factors on the chance of survival. Furthermore, patient-specific outcomes such as quality of life and post-arrest cognitive function should be investigated too.

Appendix: Table 2

Table 2: Characteristics of included studies

Author	Population	Patients (n)	Study period	Age (year, mean/ median (SD[1]/range))		Male (%)	Comorbidity pre-arrest, %)		Witnessed (%)	Shockable rhythm (%)	Time to start/SD (min)	Bystander CPR (%)	Survival to discharge/ 1-month (%)	Other (long term outcome, functional outcome, quality of life)
Ahn 2010 (22)	Adults and children	7962	2006-2007	15-64y >65y	45.2% 53.1%	65.9	NR		46.7	5.5	NR	NR	2.0*	
Applebaum 1990 (19)	NH[2] residents vs. non-residents	697	1987	82 (65-101)		NR[3]	NR		NR	NR	NR	NR	9.0*	NR
Awoke 1992 (20)	Long-term care residents	45	1987-1990	75 (64-93)		100	ASCVD[4] COPD[5] HT[6] DM[7] CVA[8] Cancer	36 33 20 20 13 4	38	27	5 min in 92%	NR	0*	NR
Bonnin 1989 (24)	Adult patients who do not regain and sustain vital signs in the field	181	1986-1987	71 (18-99)		61	NR		55	28		17	0.6	0.6% neurologically intact
Bonnin 1993 (28)	Adult patients	367	1988-1989	78.5 (18-?)		56	NR		30	32	11.3 (2-30)	17	6.5*	NR
Deasy 2011 (29)	Adult patients	7625	2000-2009	70 median (52-80)		65.5	NR		32	19	7 (6-9)	24	6.7*	NR
Fabbri 2006 (37)	Bystander witnessed CA	244	1994-2004	73 median (IQR 64-73)		66.2	MI[9] DM HT CHF[10]	24 27 26 27	100	50	5 (4-7)	NR	7.0*	7.9% favorable outcome at 1 year
Fischer 1997 (23)	Adult patients, witnessed arrest	464	1989-1992	> 70: 18-69:	46% 54%	NR	NR		62	45	16	16	15.9	7.5% of total were discharged without neurological deficit 11% of total survived to 1 year, 7.3% survived to 1 year without neurological deficit.
Gushn 1995 (17)	Patients admitted alive: Nursing home residents vs.	114	1986-1991	80.8 (±5.6)		37.5	ASCVD COPD CVA Cancer Alzheimer DM HT CRF[11]	25 22 10 11 1 17 3 2	65	17	9.3	59	10.5*	NR

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Author	Population	Patients (n)	Study period	Age (year, mean/ median (SD[1]/range))		Male (%)	Comorbidity pre-arrest, %)		Witnessed (%)	Shockable rhythm (%)	Time to start/SD (min)	Bystander CPR (%)	Survival to discharge/ 1-month (%)	Other (long term outcome, functional outcome, quality of life)
Gushn 1995 (17)	matched cohort of older community residing persons	228		80.7 (±5.6)		37.7	ASCVD COPD CVA Cancer Alzheimer DM HT CRF	55 6 10 11 3 11 10 1	77	32	9.4	34	9.2*	NR
Herlitz 2005 (16)	All patients	9067	1990-2005	71 (±12)		75	NR		68	37	6	36	4.3*	NR
Horsted 2007 (25)	Adult patients	512	2002-2004	71 (34-91) median		66.2	NR		78.5	34	NR	13.1	13.1	Survival > 6 months: 0—50 y: 14.4% 51—70 y: 17.7% 71—90 y: 7.0% > 91y: 0% In 33 survivors, median MMSE was 29 (16-30), 6 had an MMSE < 24. SF-26: 2 out of 8 aspects were significantly worse. None of the summary scores were significantly different.
Iwami 2006 (38)	Adult patients, not EMS witnessed	7962	1998-2001	70.3 (15.5)		59.4	NR		37.9	9.3	NR	NR	NR	1 year survival: 1.6% Good neurological outcome: 0.9%
Juchems 1993 (30)	Adult patients	403	1981-1989	>70 (range/ mean?)		NR	NR		NR	NR	NR	NR	10.9 *	NR
Kim 2000 (31)	Octo-genarians and nona-genarians	1300	1987-1998	80-89 >89	83% 93%	56 30	NR		48 46	31 24	46 44	46 44	9.4* 4.4*	No differences in quality of life between survivors and a matched control group.
Lombardi 1994 (26)	Adult patients	2071	1990-1991	70 median, IQR[12] 60-79)		59.3	NR		64	34	32	32	1.4	NR
Mosier 2010 (32)	Patients receiving cardio cerebral resuscitation (CCR) and ALS	1209	2005-2008	66 (±15)		67	NR		44	31	5.2 (2.3)	44	5.1*	CCR group 96.6 % of 204 survivors had good neurologic outcome, in the ALS group 85%
Murphy 1989 (21)	Patients ≥ 70 years including pts from a nursing home	244	1978-1987	70-79 80-89 90-103	51.6% 39.8% 8.6%	53.3	NR		49	25	NR	NR	0.8*	47% of survivors little/no impairment; 10.5% severely impaired; 42% moderately impaired.
Pleskot	All patients	253	2002-	77.1		65	HT		53	43	8	41	5.5*	1-y survival: 3%

Table 2: Characteristics of included studies

Author	Population	Patients (n)	Study period	Age (year, mean/ median (SD[1]/range))		Male (%)	Comorbidity pre-arrest, %)		Witnessed (%)	Shockable rhythm (%)	Time to start/SD (min)	Bystander CPR (%)	Survival to discharge/ 1-month (%)	Other (long term outcome, functional outcome, quality of life)
2010 (27)			2004	(70-97)			DM Smoking HC		28 15 8		(5.5)			At 30 days: CPC 1-2: 4.7% CPC 3-4: 0.8%
Swor 2000 (33)	Adult patients	1213	1989-1993	66.5 (±15.3, 19-112)		63.3	NR		49	50	6.1 (3.9)	20.1	5.5*	NR
Tresch 1988 (18)	Pts who were successfully resuscitated and hospitalized	613	NR	33-55 56-64 65-69 70-74 75-79 80-99	18% 22% 14% 16% 14% 15%	67.8	NR		54	44	NR	<56:76%, >56:63%	9.0*	70% Functional status unchanged; 20% deteriorated, 10% improved. 40% of survivors survived >12 months (n=4)
Tresch 1993 (36)	Nursing home patients	196	1986-1989	78.5 (31-107)		38	ASCVD HT HF Dementia MI DM CVA Pulmonary disease Cancer	52 43 42 38 26 24 21 17 10	49	20	0-15 min in 74%	NR	5.1*	70% Functional status unchanged; 20% deteriorated, 10% improved. 40% of survivors survived >12 months (n=4)
Van Hoeyweghen 1992 (34)	Adult patients	1153	1983-1987	<40 40-69 70-79 >80	8% 50% 30% 12%	NR	Functionally normal Disabled Unconscious	52 47 0.3	53	NR	8.8 (13.6)	NR	6.9 conscious at 14 days *	NR
Wuerz 1995 (35)	Patients >30 y with known initial rhythm	320	1987-1991	75 ± 7		NR	NR		59	NR	9 (5)	50 48	5.0*	NR

*Reported results only for the subgroup of older patients.
[1]Standard deviation
[2]Nursing home
[3]Not reported
[4]Atherosclerotic cardiovascular disease
[5]Chronic Obstructive Pulmonary Disease
[6]Hypertension
[7]Diabetes Mellitus
[8]Cerebrovascular accident
[9]Myocardial infarction
[10]Chronic heart failure
[11]Chronic renal failure
[12]Interquartile range

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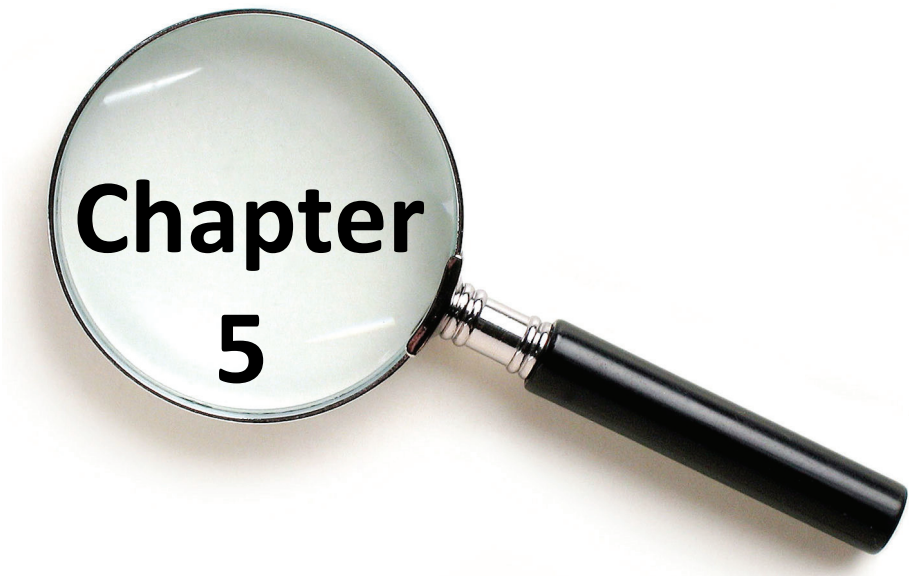

Pharmacological treatment of dementia: a scoping review of systematic reviews

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Abstract

Introduction: Until now, multiple reviews have been performed on the pharmacological treatment of dementia. We performed a scoping review to summarize research findings and to identify gaps in the existing literature.

Summary: We comprehensively searched the literature and assessed the risk of bias of the included reviews. A team of clinical experts assessed in which fields more research is needed. 55 reviews with low risk of bias were included; most of them concerned treatment of cognitive decline (n=16) and behavioral symptoms (n=10) in Alzheimer's disease (AD). Cholinesteraseinhibitors (n=13) and memantine (n=7) for cognitive impairment were most frequently described. Little information was found about the treatment of depression in dementia.

Key messages: For many current treatments there is sufficient evidence. New research should focus on symptomatic treatment of the earliest and most salient complaints in AD, and on disease-modifying interventions acting at the level of the amyloid cascade.

Introduction

Dementia is a group of chronic diseases characterized by a constant decline in the functioning of multiple cognitive domains comprising memory impairment, behavioral problems, loss of initiative, loss of independent functioning in daily activities and loss of participation in social activities. It can be due to the direct physiological effects of a general medical condition, to the persisting effects of a substance or to multiple etiologies (1). These problems with cognitive functioning decrease the quality of life of dementia patients and their caregivers, and put pressure on family relationships and friendships (2). It is a highly prevalent condition, with Alzheimer's Disease (AD) being the most common cause. The prevalence of dementia increases from 0.9% in 65- to 69-year olds to over 30% in patients aged 85 years and over (3). According to the World Health Organization the total number of people with dementia worldwide in 2010 is estimated at 35.6 million and is projected to nearly double every 20 years. Between 2000 and 2008, deaths due to AD have risen 66% in the United States (2). The population-attributable risk of AD regarding mortality over 5 years in people aged 65 years is estimated to be between 5% and 15% (4). The disease causes a high financial burden on health care services: the current global costs involved with dementia are estimated to be more than USD 600 billion per year (2).

One of the most important issues is that patients with dementia cannot be cured, but the process of cognitive deterioration can merely be delayed. In many countries, cholinesterase inhibitors and memantine are registered for the treatment of cognitive impairment in AD. Furthermore, a wide range of medication is used for the behavioral and psychological symptoms in dementia. In the past few years, a large amount of research has been published at a rapid rate concerning different aspects of the disease, ranging from diagnostic tests and treatment options to the organization of care.

To develop or practice best care, clinicians and guideline makers often use systematic reviews since they summarize available evidence in a systematic way with enhanced precision. A large number of systematic reviews on diagnostic and medical interventions for dementia are available. However, these separate systematic reviews do not directly provide overarching insights into the extent and range of established evidence in a specific field.

This scoping review was carried out for the Healthcare Insurance Board, a consulting agency that advices the Dutch government about implementing the Dutch statutory health insurance (5). The aim was to get an overview of currently registered pharmacological therapies for dementia about which systematic reviews are available. An evidence-based approach offers the most objective way to determine high quality and safety standards in clinical practice. It facilitates the process of transferring results of clinical research into practice and it has the potential to reduce healthcare costs, for example by disinvestment of ineffective practices.

In this scoping review, we provide an overview of available systematic reviews on the pharmacological treatment of the most prevalent forms of dementia and identify the field in which more research is needed.

Chapter 5

Methods

Framework scoping review

A scoping study is a relatively new methodology to systematically review an extensive body of literature that addresses a broad research question (6). While a systematic review focuses on retrieving an answer to a well-defined question, a scoping review 'maps' the relevant literature in a complete field of interest and describes only the main findings. According to Arksey and O'Malley (7), it is the nature of a scoping review not to analyze or draw conclusions. Consequently, the present work should be seen as a first step to provide an overview of existing literature and to identify the fields in which more research might be necessary in the future.

Our study comprised the following steps: identifying the clinical question, searching comprehensively for relevant reviews, appraising the quality of the reviews (with the Scottish Institute of Guidelines (SIGN) checklist), categorizing the topics of the included systematic reviews, and consultation of experts in the research fields (6;7).

Identification of reviews

We performed a systematic search for systematic reviews published in MEDLINE, EMBASE, CINAHL and PsychInfo in September 2011 and in the Cochrane Database of Systematic Reviews (CDSR) in May 2012. The search strategy was based on a search developed by Kroes et al (8). Terms for dementia were combined with names of dementia medications and the search terms were retrieved with the program PubReminer, a text mining program which gives a frequency analysis of used terms in titles and abstracts of the identified reviews (9). We used a sensitive systematic review filter of the SIGN (10) to further specify the search. The search strategy is available from the authors.

Selection of reviews

We included systematic reviews of randomized controlled trials (RCTs), clinical controlled trials (CCTs) or observational studies that investigated a pharmacological intervention for dementia. Eligible reviews should have included patients with dementia (AD, vascular dementia, Lewy Body Disease (DLB) or Parkinson dementia, frontotemporal dementia (FTD) and a category named 'unspecified dementia' that contained dementia in general or mixed forms). In addition, the review should have been published or updated between 2008 and December 2011 and written in English, French, German or Dutch and the full text article had to be accessible. For updated Cochrane Reviews, the original publication date was used. Reviews were excluded when (a) they assessed patients with mild cognitive impairment or dementia in people with Down syndrome or AIDS; (b) the medication was not registered by the European Medicines Agency (EMA) (11) or the US Food and Drug Association (FDA) (12) (e.g. experimental medications or alternative drugs) and (c) the intervention only aimed to change outcomes of caregivers. One reviewer screened the titles and abstracts of the references for eligibility, two reviewers

independently selected the full text articles. A third reviewer was consulted when the first two reviewers were uncertain about the inclusion of a review article.

Risk of bias assessment

The methodology checklist for systematic reviews and meta-analyses of the SIGN (five items) was used to assess the risk of bias of the included reviews (10). The items of this checklist were elaborated to our topic and summarized in a total estimation of the risk of bias (Table 1).

Table 1: Quality assessment of included systematic reviews

Assessment	If:
Low risk of bias ++	All 5 items were adequately addressed or well covered
Low risk of bias +	3 items were adequately addressed or well covered
High risk of bias -	Both the literature search and the quality assessment were poorly or not addressed ≥ 3 items poorly/not addressed

NB: "not applicable" was scored as neutral

A detailed description of the quality assessment is available through the authors. Two researchers independently performed the quality assessment. When necessary, disagreements were resolved through discussion with a third reviewer.

Data extraction

A standardized data-extraction form was used to systematically extract the data from reviews with low risk of bias (++ or + according to SIGN-checklist; table 1).

To provide insight in the subjects of the available systematic reviews we developed a matrix (table 2a-2d, see appendix). Each part of table 2 describes one type of dementia (unspecified dementia (including mixed types), AD, vascular dementia, FTD, Parkinson disease or DLB). Then, we categorized the medications into mechanism of action or drug class and made categories of symptoms that were addressed in the review. We put all these data in the matrix; by doing this per intervention it became clear if a systematic review was available for the outcome. The categories were approved by experts in the field. For the high quality reviews, we quoted a sentence from the abstract that summarizes the conclusion of the review (see table 3). Furthermore, we discussed the conclusions of the systematic reviews as reported by the original authors with low risk of bias per clinical feature in a narrative way.

Consultation of experts

An expert panel was involved to comment on the findings (i.e. whether they were consistent with or conflicting with current practice) and to indicate if they missed relevant

topics. In addition, we asked them which relevant practical developments for the near future they expected and for which topics they would advise future research.
Based on project time lines and cost considerations, we recruited several experts from different medical fields and geographical regions in the Netherlands. Our expert panel, composed of a neurologist, a psychiatrist, a specialist for internal medicine, a geriatrician and a caregiver of a dementia patient, commented on the steps in several phases of the review process by email and by personal communication. These expert-based comments were added to the overview of systematic reviews.

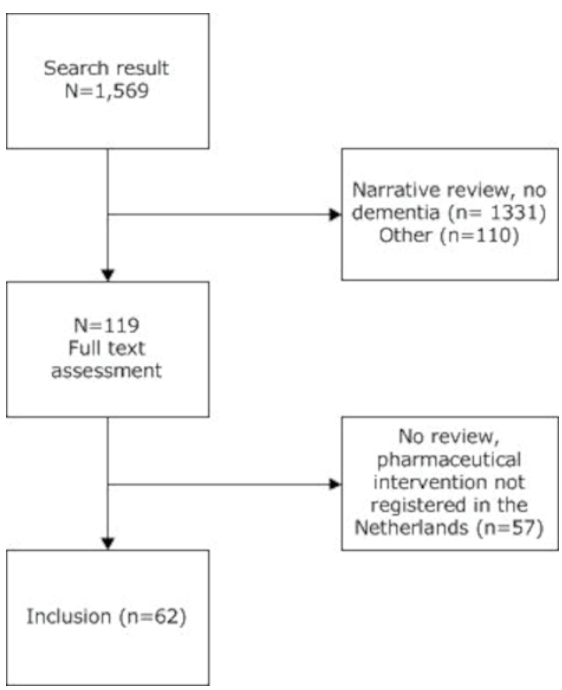
Results

The findings are presented as an overview of available systematic reviews and the fields in which more research is needed. Some reviews are mentioned more than once, because they cover more than one topic. More details of reviews included in this scoping study can be obtained from the authors.

Identification of studies

The search yielded 1,569 records. Based on title and abstract, we read the full texts of 117 articles. Finally, 62 articles, including 34 Cochrane reviews, fulfilled the predefined inclusion criteria (Figure 1).

Figure 1: Flowchart of included studies



The most prevalent reason for excluding a review was that the reported intervention was not FDA- or EMA-registered. Out of the 62 reviews, 55 (90%) reviews were assessed as having a low risk of bias. To describe the results, only the reviews with low risk of bias were used.

Risk of bias assessment

Out of 62 reviews, seven reviews were considered as having high risk of bias due to multiple flaws in the methodology (figure 1). 55 scored a low risk of bias (++ or + according to SIGN-checklist). Of these, 34 received '++' and 21 received '+'. However, 13 of the '+' reviews lacked an assessment of the risk of bias of included studies, which means that the conclusions of these reviews are less reliable. The 55 low risk of bias reviews can be found in table 2.

Description of included reviews with low risk of bias

The 55 reviews with low risk of bias addressed mainly the fields of Alzheimer (n=22) and unspecified dementia (including mixed forms) (n=29) (table 2a-b). Surprisingly, treatment for Parkinson dementia/DLB and vascular dementia was assessed in only 3 and 6 reviews, respectively, and frontotemporal dementia in none (table 2c-d). The numbers increased to over 56 because some reviews addressed more than one type of dementia (13-15). Most included reviews reported cognitive decline (n=33), behavioral symptoms (n=21) and adverse events (n=26) as primary outcomes.

Cognitive decline

<u>Alzheimer's disease and Parkinson's dementia/DLB</u>

For cognitive decline in Alzheimer's disease, 17 reviews were available. The reviews by Birks et al. (16-18) showed that cholinesterase inhibitors are efficacious for mild to moderate AD, as well as for Parkinson's dementia (19;20), and they are cost-effective (17;21). With regard to the effects, the different drugs are comparable, but with respect to the side effects donepezil might be the better choice (22).

Memantine proved to be effective for patients with moderate to severe AD, although not for other forms of dementia (23). For many interventions, such as aspirin, steroids and NSAIDs (24-27), nicotine (28), hormone replacement (29) and thiamine (30) the evidence for an effect on cognitive decline is limited because of lack of studies of high methodological quality and sufficient power. For ginkgo biloba the results are conflicting (13;31), although it appears to be safe (32)

<u>Vascular dementia</u>

For vascular dementia, the efficacy of galantamine has been tested in two studies that found some evidence of benefit, whereas the other study did not find clear advantage over the placebo (33). For rivastigmine no proper randomized controlled trials were

available (34). Therefore, cholinesterase inhibitors cannot be recommended for vascular dementia.

Unspecified dementia

Nine reviews about cognitive decline in unspecified dementia were identified. For antihypertensives, there are indications that they are beneficial (14;35). No evidence was found to support the use of piracetam (36), melatonin (37), vitamins (38-40), statins (41), and antidepressive agents (42).

Behavioral problems

For this topic, no distinction for type of dementia was made. Twenty-seven systematic reviews described interventions for behavioral problems such as agitation, aggression and behavioral and psychological symptoms of dementia (BPSD) in dementia. According to McShane et al, the use of memantine resulted in a consistent, small reduction in the incidence of agitation (43) in demented patients. However, there was no available evidence addressing the question as to whether prevalent agitation can be treated with memantine. No studies or only studies of low methodological quality were available for pain medication (44;45). Further studies are needed to establish the efficacy of cyproterone (46). There is an effect of melatonin in sundowning in demented patients (47), but trazodone (48), valproate (49) and haloperidol (50) have not shown any treatment effect for agitation among demented patients, whereas they have potential side effects (51-53).

Neuropsychiatric symptoms

For this topic, no distinction for type of dementia was made. Eight reviews described neuropsychiatric symptoms, such as hallucinations and delusions. No evidence was found for an effect of anticonvulsant mood stabilizers (54) and second generation antipsychotics (SGAs) (53). Moreover, SGAs increase the risk of falling in nursing home residents (51) and of cerebrovascular events (52). Two reviews found that antidepressants can be effective in the treatment of BPSD (55;56), whereas Martinón et al. found no effect of trazodone.

Depression

The number of reviews about depression in demented patients is scarce. Only one review showed weak support that antidepressants are effective for patients with depression and dementia (type not specified) (42).

Patient-centered outcomes

Activities of daily living, institutionalization and quality of life, although important from a patient's point of view, were only investigated as secondary outcomes. Tables 2a-2d shows the reviews describing these outcomes.

Table 2a: Description of the available evidence with low risk of bias for unspecified dementia

Medical treatment (number of reviews)	Behavioral symptoms[1]	Neuropsychiatric symptoms[2]	Adverse events	Cognitive decline	Depression	Sleep Disorders	ADL/ institutionalization	Morbidity	Quality of life	Other
Analgesic agents (n=1)	Husebo 2011 (44), Kim 2008 (45)									
Anticonvulsive agents (n=2)	Konovalov 2008 (54)	Konovalov 2008 (54)	Lonergan 2009 (49)			Konovalov 2008 (54)				
Antidepressive agents (n=5)	Henry 2011 (56) ; Seitz 2011 (55) ; Martinón 2004 (48)	Seitz 2011 (55)	Seitz 2011 (55);Bains 2002 (42); Sterke 2008 (51)	Bains 2002 (42)	Bains 2002 (42)	Henry 2011 (56)				
Anti-hypertensive agents (n=2)			Birks 2002 (35)	Birks 2002 (35); Shah 2009 (14)			Birks 2002 (35)			
Antipsychotic agents (n=4)	Gentile 2010 (53); Lonergan 2002 (50)	Gentile 2010 (53)	Sterke 2008 (51); Mittal 2011 (52); Gentile 2010 (53);							
Benzodiazepines (n=1)			Sterke 2008 (51)							
Fatty acids / nutritional supplements (n=1)							Hanson 2011 (65)	Hanson 2011 (65)	Hanson 2011 (65)	Weight; mortality; pressure ulcer healing: Hanson 2011 (65)
Ginkgo biloba (n=1)	Birks 2009 (31); Weinmann 2010 (13)		Birks 2009 (31); Weinmann 2010 (13)	Birks 2009 (31); Weinmann 2010 (13)			Birks 2009 (31); Weinmann 2010 (13)		Birks 2009 (31); Weinmann 2010 (13)	
Hormone therapy (n=2)	Guay 2008 (66)		Bolea 2011 (46)		Hogervorst 2009 (67)					
Memantine (n=1)	McShane 2006 (43)	McShane 2006 (43)	McShane 2006 (43)	McShane 2006 (43)			McShane 2006 (43)			
Piracetam (n=1)				Flicker 2004 (36)						
Melatonin (n=2)	De Jonghe 2010 (47); Jansen 2006 (37)			Jansen 2006 (37)	Jansen 2006 (37)	De Jonghe 2010 (47); Jansen 2006 (37)				
Statins (n=1)	McGuinness 2010 (41)		McGuinness 2010 (41)	McGuinness 2010 (41)			McGuinness 2010 (41)		McGuinness 2010 (41)	
Vitamins/ minerals (n=3)				Malouf 2008 (40), Malouf 2003a (38); Malouf 2003b (39)						

[1]Includes sexual misbehavior, wandering, aggression and agitation and behavioral and psychological symptoms of dementia (BPSD)/ [2]Includes psychiatric complaints such as anxiety, psychosis and delusions

Table 2b: Description of the available evidence with low risk of bias for Alzheimer's disease

Medical treatment (number of reviews)	Behavioral symptoms	Neuropsychiatric symptoms	Adverse events	Cognitive decline	Depression	Sleep Disorders	ADL/ institutionalization	Morbidity	Quality of life	Other
Analgesic agents (n=1)	Kim 2008 (45)	Kim 2008 (45)								
Anti-depressive agents (n=1)						Salami 2011 (29)				
Anti-hypertensive agents (n=1)				Shah 2009 (14)						
Anti-psychotic agents (n=1)						Salami 2011 (29)				
Aspirin / NSAIDs (n=4)	Jaturapatporn 2012 (24)		Tabet 2002 (25); Tabet 2003 (26); Thoonsen 2010 (27); Jaturapatporn 2012 (24)	Tabet 2002 (25); Tabet 2003 (26); Thoonsen 2010 (27); Jaturapatporn 2012 (24)	Jaturapatporn 2012 (24)		Jaturapatporn 2012 (24)			Death, clinical global impression of change, caregiver burden : Jaturapatporn (24)
Cholin-esterase inhibitors (n=7)	Birks 2006a (16); Birks 2006b (17); Birks 2009 (18); Rodda 2009 (68)		Birks 2006a (16); Birks 2006b (17); Birks 2009 (18); Lockhart 2009 (22)	Birks 2006a (16); Birks 2006b (17); Birks 2009 (18); Cappell (21)		Salami 2011 (29)	Birks 2006a (16); Birks 2006b (17); Birks 2009 (18)			Cost-effectiveness: Birks 2006b (17) Apathy: Rodda 2009 (68)
Ginkgo biloba (n=2)	Weinmann 2010 (13)		Weinmann 2010 (13); Man 2008 (32)	Weinmann 2010 (13)	Weinmann 2010 (13)		Weinmann 2010 (13)		Weinmann 2010 (13)	
Hormone therapy (n=1)						Salami 2011 (29)				
Memantine (n=5)	Grossberg 2009 (69) ; Maidment 2008 (15)	Grossberg 2009 (69)		Cappell 2010 (21); McKeage 2009 (23); Schneider 2011 (70)			McKeage 2009 (23); Schneider 2011 (70)			Cost effectiveness: Cappell 2010 (21); McKeage 2009 (23)
Selegiline (n=1)			Birks 2003 (71)	Birks 2003 (71)					Birks 2003 (71)	
Nicotine (n=1)				López 2001 (28)						
Vitamins/ minerals (n=2)	El-Kareem-Nasr 2008 (72)			El-Kareem-Nasr 2008 (72); Rodríguez 2001 (30)			El-Kareem-Nasr 2008 (72)			
Steroidal (n=1)	Jaturapatporn 2012 (24)		Jaturapatporn 2012 (24)	Jaturapatporn 2012 (24)	Jaturapatporn 2012 (24)		Jaturapatporn 2012 (24)			Death, clinical global impression of change, caregiver burden : Jaturapatporn 2012 (24)

Table 2c: Description of the available evidence with low risk of bias for Parkinson's dementia and Lewy Body Disease

Medical treatment (number of reviews)	Behavioral symptoms	Neuropsychiatric symptoms	Adverse events	Cognitive decline	Depression	Sleep Disorders	ADL/ institutionalization	Morbidity	Quality of life	Other
Cholinesterase inhibitors (n=3)		Rolinski 2012 (20)	Rolinski 2012 (20); Maidment 2006 (19); Wild 2003 (73)	Rolinski 2012 (20); Maidment 2006 (19);			Rolinski 2012 (20); Maidment 2006 (19);		Rolinski 2012 (20)	Global assessment, effect on carers, effect on Parkinson features, death, health economics: Rolinski 2012 (20)

Table 2d: Description of the available evidence with low risk of bias for vascular dementia

Medical treatment (number of reviews)	Behavioral symptoms	Neuropsychiatric	Adverse events	Cognitive decline	Depression	Sleep Disorders	ADL/ institutionalization	Morbidity	Quality of life	Other
Antidepressive agents (n=1)				Levine 2011 (74)						
Antihypertensive agents (n=2)	Levine 2011 (74)			Shah 2009 (14)						
Aspirin / NSAIDs (n=1)				Levine 2011 (74)						Prevention: Levine 2011 (74)
Cholinesterase inhibitors (n=4)	Craig 2005 (34)		Craig 2005 (34) ; Craig 2006 (33); Malouf 2004 (75)	Craig 2005 (34); Craig 2006 (33); Malouf 2004 (75)			Craig 2005 (34); Malouf 2004 (75)			
Ginkgo biloba (n=1)	Weinmann 2010 (13)		Weinmann 2010 (13)	Weinmann 2010 (13)			Weinmann 2010 (13)		Weinmann 2010 (13)	
Memantine (n=1)				Levine 2011 (74)						
Statins (n=1)										Prevention: Levine 2011 (74)
Vitamins/minerals (n=1)										Prevention: Levine 2011 (74)

Expert panel survey results

The expert panel commented on the matrix (Table 2a-2d) and on the conclusions of the reviews (Table 3). Furthermore, we asked them about promising interventions and implications for further research regarding the pharmacological treatment of dementia.

There are sufficient systematic reviews about the efficacy of cholinesterase inhibitors for cognitive impairment mild-to-moderate stadia of AD and Parkinson's dementia, which are most frequently used in current practice. In addition, various systematic reviews about the efficacy of memantine on cognition are available. For several other interventions, such as NSAIDs, selegiline and hormone replacement, there is sufficient evidence to show that these are not effective.

Table 3a: Overview of included studies, unspecified dementia (n=29)

Author	Investigated treatment	Quote
Bains 2002 (42)	Antidepressants	'Available evidence offers weak support to the contention that antidepressants are effective for patients with depression and dementia. However, only four studies are included in the meta-analysis relating to efficacy, and sample sizes are small. Moreover, only two included studies investigated the properties of the more commonly used SSRIs and no studies investigated the properties of newer classes of antidepressants (e.g. selective noradrenergic reuptake inhibitors). This review draws attention to the paucity of research and evidence in this area.'
Birks 2002 (35)	Nimodipine	'Nimodipine can be of some benefit in the treatment of patients with features of dementia due to unclassified disease or to Alzheimer's disease, cerebrovascular disease, or mixed Alzheimer's and cerebrovascular disease. It appears to be well tolerated with few side effects. Data were not available from several trials, a total of more than 500 patients. A meta-analysis of individual patient data from all trials is desirable. Dementia is a chronic disorder and the short-term benefits of nimodipine demonstrated in the trials reviewed do not justify its use as a long-term anti-dementia drug. New research must focus on longer term outcomes.'
Birks 2009b (31)	Ginkgo biloba	'Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.'
Bolea 2011 (46)	Cyproterone	'Despite there being evidence to support our observations of a useful role for cyproterone in aggressiveness in dementia, further studies are needed to establish the efficacy and safety of this therapeutic option.'
De Jonghe 2010 (47)	Melatonin	'Sundowning/agitated behaviour improves with melatonin treatment in patients with dementia.'
Flicker 2004 (36)	Piracetam	'Published evidence does not support the use of piracetam in the treatment of people with dementia or cognitive impairment. Although effects were found on global impression of change, no benefit was shown by any of the more specific measures of cognitive function.'
Gentile 2010 (53)	Second-generation antipsychotics (SGAs)	'Because of their undemonstrated effectiveness, SGAs should be avoided in patients with dementia complicated by psychotic and/or behavioural symptoms. Hence, further researches are urgently needed to identify useful pharmacological strategies that can be used to improve the clinical condition of such patients and to reduce burden to caregivers when behavioural interventions are ineffective.'
Guay 2008 (66)	Treatments for inappropriate sexual behavior	'In general, unless the patient is engaging in or threatening dangerous acts involving physical contact, serotoninergics (first choice, SSRIs; second choice, TCAs) are first-line agents (for abnormal sexual behavior) followed by antiandrogens (cyproterone acetate or medroxyprogesterone acetate) as second-line agents. LHRH agonists (first choice) and estrogens (second choice) are considered third-line agents. Combination therapy is reasonable if the patient fails to respond to monotherapy.'
Hanson 2011 (65)	Oral feeding, feeding supplements	'High-calorie supplements are an evidence-based option to promote weight gain for people with dementia and feeding problems. Assisted feeding, appetite stimulants, and modified foods may also improve weight, and treatments can be used individually or in combination. Based on current evidence, specialized oral feeding interventions are unlikely to change how people with dementia function or how long they live.'
Henry 2011 (56)	Antidepressants	'This review indicates that antidepressants can be effective in the treatment of BPSD and are generally well tolerated in elderly demented patients.'
Hogervorst 2009 (67)	Hormone replacement therapy	'Currently, hormone replacement therapy (HRT) or estrogen replacement therapy (ERT) for cognitive improvement or maintenance is not indicated for women with Alzheimer Dementia.'
Husebo 2011 (44)	Pain treatment	'There is a profound dearth of rigorous studies of the effect of pain treatment in patients with dementia and agitation. The available studies do not support the hypothesis that pain management reduces agitation in nursing-home patients with dementia. Randomized, controlled parallel-group studies are needed.'
Jansen 2006 (37)	Melatonin	'The analyses did not support the use of melatonin for treatment of cognitive impairment associated with dementia. Meta-analysis of psychopathologic behavior scale scores suggested that melatonin may be effective in treating these dementia-related disturbances.'
Konavolov 2008 (54)	Anticonvulsant mood stabilizers	'Although clearly beneficial in some patients, anticonvulsant mood stabilizers cannot be recommended for routine use in the treatment of BPSD at the present time.'
Lonergan 2002 (50)	Haloperidol	'No evidence has been found of any significant general improvement in manifestations of agitation, other than aggression, among demented patients treated with haloperidol, compared with controls.'
Lonergan 2009 (49)	Valproate	'Valproate preparations are ineffective in treating agitation among demented patients, and that valproate therapy is associated with an unacceptable rate of adverse effects.'
Maidment 2008 (15)	Memantine	'Memantine decreases NPI scores and may have a role in managing BPSD. However, there are a number of limitations with the current data; the effect size was relatively small, and whether memantine produces significant clinical benefit is not clear.'

Table 3a: Overview of included studies, unspecified dementia (n=29)

Author	Investigated treatment	Quote
Malouf 2003a (39)	Vitamin B12	'Vitamin B12 is essential for maintaining normal function of the nervous system, but the relationship between vitamin B12 and cognitive function is not fully understood. From the three studies involving people with dementia or cognitive impairment and low blood levels of vitamin B12 eligible for inclusion in this review there was no statistically significant effect of vitamin B12 supplementation on cognition. The variety of measurement scales used to assess outcomes and uncertainty about diagnostic criteria for vitamin B12 deficiency create difficulties in pooling the results of trials.'
Malouf 2003b (38)	Vitamin B6	'This review found no evidence for short-term benefit from vitamin B6 in improving mood (depression, fatigue and tension symptoms) or cognitive functions. For the older people included in one of the two trials included in the review, oral vitamin B6 supplements improved biochemical indices of vitamin B6 status, but potential effects on blood homocysteine levels were not assessed in either study. This review found evidence that there is scope for increasing some biochemical indices of vitamin B6 status among older people. More randomized controlled trials are needed to explore possible benefits from vitamin B6 supplementation for healthy older people and for those with cognitive impairment or dementia.'
Malouf 2008 (40)	Folic acid with or without vitamin B12	'The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people.'
Martinón 2004 (48)	Trazodone	'There is insufficient evidence to recommend the use of trazodone as a treatment for behavioural and psychological manifestations of dementia. In order to assess effectiveness and safety of trazodone, longer-term randomized controlled trials are needed, involving larger samples of participants with a wider variety of types and severities of dementia.'
McGuinness 2010 (41)	Statins	'There is insufficient evidence to recommend statins for the treatment of dementia. Analysis from the studies available, including one large RCT, indicate statins have no benefit on the outcome measures ADAS-Cog or MMSE. We need to await full results from CLASP 2008[1] before we can be certain. This Cochrane review will be updated as these results become available.'
McShane 2006 (43)	Memantine	'Memantine has a small beneficial effect at six months in moderate to severe Alzheimer Dementia. In patients with mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with vascular dementia and was detectable in those with AD. Memantine is well tolerated.'
Mittal 011 (52)	Antipsychotics	'Although some psychotropic medications have shown modest efficacy in the treatment of these behaviors, their use has generated controversy due to increasing recognition of the side effects of these medications especially the antipsychotic medications (…). Available evidence indicates that antipsychotic medications increase the risk of cerebrovascular adverse events and death when used to treat elderly patients with Behavioral and Psychological Symptoms of Dementia.'
Seitz 2011 (55)	Antidepressants	'The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics.'
Shah 2009 (14)	Antihypertensives	'Antihypertensive medications—particularly ACE inhibitors and diuretics—may be helpful in reducing the risk for and progression of dementia. Large randomized clinical trials are warranted to further explore the relationship between antihypertensive drugs and dementia.'
Sterke 2008 (51)	Psychoactive drugs, antidepressants, anti-anxiety drugs	'Research on the contribution of psychoactive drugs to fall risk in nursing home residents with dementia is limited. The scarce evidence shows, however, that multiple drugs, antidepressants and anti-anxiety drugs increase fall risk in nursing home populations with residents with dementia.'
Weinmann 2010 (13)	Ginkgo biloba	'Ginkgo biloba appears more effective than placebo. Effect sizes were moderate, while clinical relevance is, similar to other dementia drugs, difficult to determine.'

[1] CLASP 2008 Sano M. Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Simvastatin to Slow the Progression of Alzheimer's Disease. ICAD abstracts. 2008.

Furthermore, the panel was asked which topics they missed in current literature on dementia. Little is known about the combination of cholinesterase inhibitor therapy with memantine, although recently a primary study has been published on this topic (57). Neither is it known whether cholinesterase inhibitors are effective in combination with other drug types, such as antihypertensive drugs. Furthermore, which cholinesterase inhibitor is preferable in the light of its efficacy and side effects is still a topic of discussion, and little evidence is available regarding the continuation or discontinuation of these medications when the disease progresses (57). Therefore, our expert team suggested that

comparative effectiveness research should be performed instead of more placebo-controlled trials on these types of drug therapy.

It is striking that often drugs are prescribed for symptoms of demented patients, while aggregated evidence is lacking. For example, few reviews were published considering the treatment of depression in dementia although depression is highly prevalent in dementia (58). In addition, although epidemiological studies show that the numbers of patients with AD affected by delirium vary from 22% to 89% in the community and hospitalized populations (59), it is another striking example of a syndrome that is hardly studied in these patients. Likewise, few reviews addressed the ability of patients to live independently or to perform their activities of daily living without help, although these outcomes are likely to be meaningful for patients as well as their caregivers (60).

New research should focus on symptomatic treatment of the earliest and most salient complaints in AD and on disease-modifying interventions acting at the level of the amyloid cascade. Promising nutritional interventions, immunotherapy acting at the level of the amyloid cascade, drugs that target tau, progranulin or TDP 43 are all missing in this overview, because these interventions are not yet registered for clinical use or are still in the development phase (61). Logically, systematic reviews on these topics have not been performed yet.

Table 3b: Overview of included studies, Alzheimer's disease (n=22)

Author		Quote
Birks 2003 (71)	Selegiline	'Despite its initial promise, i.e. the potential neuroprotective properties, and its role in the treatment of Parkinson's disease, selegiline for Alzheimer's disease has proved disappointing. Although there is no evidence of a significant adverse event profile, there is also no evidence of a clinically meaningful benefit for people with Alzheimer's disease. There would seem to be no justification, therefore, to use it for Alzheimer's disease, nor for any further studies of its efficacy in Alzheimer's disease.'
Birks 2006a (16)	Cholinesterase inhibitors	'The three cholinesterase inhibitors are efficacious for mild to moderate Alzheimer's disease. Despite the slight variations in the mode of action of the three cholinesterase inhibitors there is no evidence of any differences between them with respect to efficacy. The evidence from one large trial shows fewer adverse events associated with donepezil compared with rivastigmine.'
Birks 2006b (17)	Donepezil	'There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total health care resource costs. Benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose. Taking into consideration the better tolerability of the 5 mg/day donepezil compared with the 10 mg/day dose, together with the lower cost, the lower dose may be the better option. The debate on whether donepezil is effective continues despite the evidence of efficacy from the clinical studies because the treatment effects are small and are not always apparent in practice, and because of the cost of the drug.'
Birks 2009a (18)	Rivastigmine	'Rivastigmine appears to be beneficial for people with mild to moderate Alzheimer's disease. In comparisons with placebo, improvements were seen in the rate of decline of cognitive function, activities of daily living, and severity of dementia with daily doses of 6 to 12 mg. Adverse events were consistent with the cholinergic actions of the drug. A transdermal patch has been tested in one trial, and there is evidence that the lower dose smaller patch is associated with fewer side effects than the capsules or the higher dose larger patch and has comparable efficacy to both. This review has not examined economic data.'
Cappell 2010 (21)	Donepezil, memantine, galantamine, rivastigmine	'When viewed from the social perspective, pharmacotherapy (donepezil, memantine, galantamine, rivastigmine) has the potential to reduce the economic burden of the illness, even in later stages of this disease, though more rigorous pharmacoeconomic studies are still needed.'
El Kasreem Nasr 2008 (72)	Vitamin E	'This review found no evidence for efficacy of vitamin E in the treatment of AD. Taken together with other evidence that vitamin E, especially in the large doses used in the included studies, may be associated with potentially significant side effects and even an increased rate of all-cause mortality, we conclude that vitamin E should not be used in the treatment of AD.'
Grossberg 2009 (69)	Memantine	'Overall, patients who received memantine performed better on behavioral measures than those treated with placebo.'

Table 3b: Overview of included studies, Alzheimer's disease (n=22)

Author		Quote
Jaturapatporn 2012 (24)	NSAID	'Based on the studies carried out so far, the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven. Therefore, these drugs cannot be recommended for the treatment of AD.'
Kim 2008 (45)	Gabapentin	'The dearth of available data limits support for the off-label use of gabapentin for the treatment of BPSD. Furthermore, controlled studies should be conducted before gabapentin can be clinically indicated for the successful treatment of BPSD.'
Lockhart 2009 (22)	Donepezil, rivastigmine, galantamine	'Subjects with mild to moderate AD treated in routine clinical practice with donepezil were more adherent to pharmacotherapy, and had a lower risk of gastrointestinal adverse effects compared with rivastigmine or galantamine. This finding accords with results reported in the randomised clinical trial literature.'
López 2001 (28)	Nicontine	'This review is not able to provide any evidence that nicotine is or is not a useful treatment for Alzheimer´s disease.'
Man 2008 (32)	Ginkgo biloba	'Among various herbal medicines (HMs), the safety and tolerability of Ginkgo biloba was best established. Further multi-center trials with large sample size, high methodological qualities and standardized HM ingredients are necessary for clinical recommendations on the use of HM in treating AD.'
Maidment 2008 (15)	Memantine	'Memantine decreases NPI scores and may have a role in managing BPSD. However, there are a number of limitations with the current data; the effect size was relatively small, and whether memantine produces significant clinical benefit is not clear.'
McKeage 2009 (23)	Memantine	'In the management of patients with moderate to severe Alzheimer's disease, memantine provides an effective treatment option. To date, clinical trial support is greater for memantine use in combination with an AChE inhibitor, while more data are needed to confirm its efficacy as monotherapy.'
Rodda 2009 (68)	Cholinesterase inhibitors	'The evidence is limited, in part due to methodological considerations. In the absence of alternative safe and effective management options, the use of cholinesterase inhibitors is an appropriate pharmacological strategy for the management of BPSD in Alzheimer's disease.'
Rodríguez 2001 (30)	Thiamine	'It is not possible to draw any conclusions from this review. The number of people included in the studies is less than 50 and the reported results are inadequate.'
Salami 2011 (29)	Treatments targeting sleep disturbance	'Most current treatments targeting sleep disturbance in Alzheimer's dementia are ineffective. There is a need for further investigation of interventions for treating sleep disturbance in Alzheimer's dementia.'
Schneider 2011 (70)	Memantine	'Despite its frequent off-label use, evidence is lacking for a benefit of memantine in mild AD, and there is meager evidence for its efficacy in moderate AD.'
Shah 2009 (14)	Anti-hypertensive medications	'Antihypertensive medications—particularly ACE inhibitors and diuretics—may be helpful in reducing the risk for and progression of dementia. Large randomized clinical trials are warranted to further explore the relationship between antihypertensive drugs and dementia.'
Tabet 2002 (25)	Indomethacin	'On the basis of this one trial and subsequent analysis of data as reported by the authors, indomethacin cannot be recommended for the treatment of mild to moderate severity Alzheimer's disease. At doses of 100-150 mg daily, serious side effects will limit its use.'
Tabet 2003 (26)	Ibuprofen	'No evidence yet exists from randomized double-blind and placebo-controlled trials on whether ibuprofen is efficacious for patients diagnosed as having Alzheimer's disease. Ibuprofen, like other NSAIDs, has an identifiable and in some instances a significant side-effect profile which may include gastrointestinal bleeding. Therefore, it needs to be shown that the benefits of such a treatment outweigh the risk of side effects before ibuprofen can be recommended for people with Alzheimer's disease.'
Thoonsen 2010 (27)	Aspirin	'Although the number of cases in both trials is small, our findings suggest that aspirin use in AD might pose an increased risk of intracerebral hemorrhages (ICH), whereas it has no effect on cognition. If there is an unequivocal cardiovascular indication for aspirin, it should not be withheld in AD patients.'
Weinmann 2010 (13)	Ginkgo biloba	'Ginkgo biloba appears more effective than placebo. Effect sizes were moderate, while clinical relevance is, similar to other dementia drugs, difficult to determine.'

Table 3c: Overview of included studies, Parkinson's dementia/DLB (n=3)

Author		Quote
Maidment 2006 (19)	Cholinesterase inhibitors	'Dementia is frequently associated with Parkinson's Disease. While a number of neurotransmitters appear to be involved, loss of cholinergic functioning is particularly associated with Parkinson's Disease Dementia (PDD) suggesting a potential utility for cholinesterase inhibitors. Rivastigmine appears to moderately improve cognition and to a lesser extent activities of daily living in patients with PDD. There was a clinically meaningful benefit in 15% of patients. Efficacy in other domains requires confirmation. Tolerability in particular nausea, vomiting and tremor appear problematic.'
Rolinski 2012 (20)	Cholinesterase inhibitors	'The currently available evidence supports the use of cholinesterase inhibitors in patients with PDD, with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales. The effect in DLB remains unclear. There is no current disaggregated evidence to support their use in CIND-PD.'
Wild 2003 (73)	Rivastigmine	'Patients with dementia with Lewy bodies who suffer from behavioural disturbance or psychiatric problems may benefit from rivastigmine if they tolerate it, but the evidence is weak. Further trials using rivastigmine are needed, as are trials of other cholinesterase inhibitors in dementia with Lewy bodies.'

Table 3d: Overview of included studies, vascular dementia (n=6)

Author		Quote
Craig 2005 (34)	Rivastigmine	'Although existing trial data indicated some benefit of rivastigmine in vascular cognitive impairment (VCI), these were derived from studies which had small numbers of patients, and which compared rivastigmine to treatments other than placebo or extrapolated results post hoc from large studies involving patients with Alzheimer's disease and vascular risk factors of unclear significance. They could not be included in this review. Proper randomized placebo-controlled double-blind trials involving patients with VCI are needed before any conclusions regarding the use of rivastigmine in VCI can be drawn.'
Craig 2006 (33)	Galantamine	'The efficacy of galantamine has been tested in two RCTs for the treatment of vascular dementia and for a mixed population of Alzheimer's disease patients with evidence of cerebrovascular disease. The rationale behind its use is to correct the cholinergic deficit seen in vascular dementia. This review found evidence of benefit in measures of cognition including executive functioning in one study but no clear advantage over placebo in another study when patients with pure vascular dementia were considered. Both studies indicated higher rates of nausea and vomiting in actively treated participants.'
Levine 2011 (74)	Pharmacologic & nonpharmacologic interventions for vascular dementia	This is a very broad overview article; no general conclusion can be made.
Malouf 2004 (75)	Donepezil	'Evidence from the available studies supports the benefit of donepezil in improving cognition function, clinical global impression and activities of daily living in patients with probable or possible mild to moderate vascular cognitive impairment after 6 months treatment. Extending studies for longer periods would be desirable to establish the efficacy of donepezil in patients with advanced stages of cognitive impairment. Moreover, there is an urgent need for establishing specific clinical diagnostic criteria and rating scales for vascular cognitive impairment.'
Shah 2009 (14)	Antihypertensive medications	'Antihypertensive medications—particularly ACE inhibitors and diuretics—may be helpful in reducing the risk for and progression of dementia. Large randomized clinical trials are warranted to further explore the relationship between antihypertensive drugs and dementia.'
Weinmann 2010 (13)	Ginkgo biloba	'Ginkgo biloba appears more effective than placebo. Effect sizes were moderate, while clinical relevance is, similar to other dementia drugs, difficult to determine.'

Discussion

We performed a scoping review that aimed to give an overview of the subjects and methodological quality of the currently available systematic reviews on the pharmacological treatment of the most prevalent forms of dementia. In addition, it identifies gaps in the existing literature and facilitates dissemination.

Our scoping review is the first systematic overview of recent systematic reviews regarding the pharmacological treatment of dementia. It shows that in the field of dementia most research is done about the effects of cholinesterase inhibitors, NMDA-receptor antagonists and antipsychotics (table 2). Furthermore, is also indicates that for many indications, no systematic review is available. Without aggregated evidence, it is difficult and time-consuming to provide evidence-based care to patients.

Several topics, such as the treatment of cognitive impairment in AD with cholinesterase inhibitors, have been thoroughly studied over the past few years. Starting up new projects on these topics is of little value. Head-to-head comparison trials to find out which intervention is best and also investigations to find out when to discontinue this type of intervention are of greater interest for future research. Such research might better be performed as coordinated international prospective cohort studies in daily practice, as RCTs are expensive and time-consuming.

Many reviews about the treatment of behavioral problems have been published. From the available systematic reviews it appeared that these kinds of symptoms are very difficult to treat with medication; moreover, currently used therapies such as antipsychotics have major side effects. Perhaps the management of these problems should rather be non-

pharmacological, with interventions such as environmental modification, task simplification and appropriate activities (62;63).

Our scoping review has a number of strengths. First, it provides a broad overview of both the recent available systematic reviews and the gaps in the literature concerning the pharmacological treatment of dementia. Second, we performed an extensive search in several databases; thereby, the chance of missing relevant publications was reduced. Furthermore, two independent assessors selected the reviews and assessed the risk of bias, thereby which reduced the chance of errors.

However, there are some limitations worth noting. Although in general the quality of systematic reviews in the field of pharmacological treatment options for dementia was high, the quality assessment of the primary studies was lacking in many cases. Whether the results of a systematic review can be relied on for clinical practice depends on two factors: its own risk of bias and the risk of bias of the included studies. It has been shown that even systematic reviews published in leading journals often have important methodological limitations, potentially leading to biased results and different answers to the same question (64). However, we have chosen to extract the data from these reviews as well because apart from this item, the reviews had been performed well and no alternative evidence with smaller risk of bias was available.

For identifying the gaps in the literature, we relied on the expert panel. Although this expert panel consisted of prominent professionals from different branches involved in the treatment and care of demented patients, expert opinions are also dependent of personal interests and knowledge. Besides, all experts originated from the Netherlands.

We have summarized the results in a narrative way and thereby relied on the reports of the authors. Checking the size of the effect and assessing its clinical relevance was beyond the scope of this overview. We checked for the presence of results regarding efficacy by looking at evidence from placebo-controlled trials and for evidence regarding the difference in effect between various drugs. We also looked for evidence regarding side effects, but other factors such as pharmacoeconomics and implementation research are not described. Furthermore, because the aim of this scoping review was to give an overview of available reviews, new and unregistered medication is not reported. However, we have covered this topic in the expert opinion part.

Conclusion

This scoping review is a comprehensive overview of the currently available systematic reviews on the pharmacological treatment of dementia and therefore, is a starting-point for clinicians and guideline-developers to find systematic reviews regarding various pharmacological treatments for dementia. It shows the gaps in the existing literature and indicates where future reviews and/or primary research might be necessary. When used as a starting point for guideline development, not only treatment effects are necessary. It is also important to know if the identified evidence is applicable to the patients for whom the guideline is directed to (e.g. by looking at the results of comparative effectiveness

research) and to consider other factors such as the patient perspective, available resources and local circumstances. Finally, this scoping review may guide the development of quality indicators, which are more and more used in implementing guidelines and assessing added value of treatment components.

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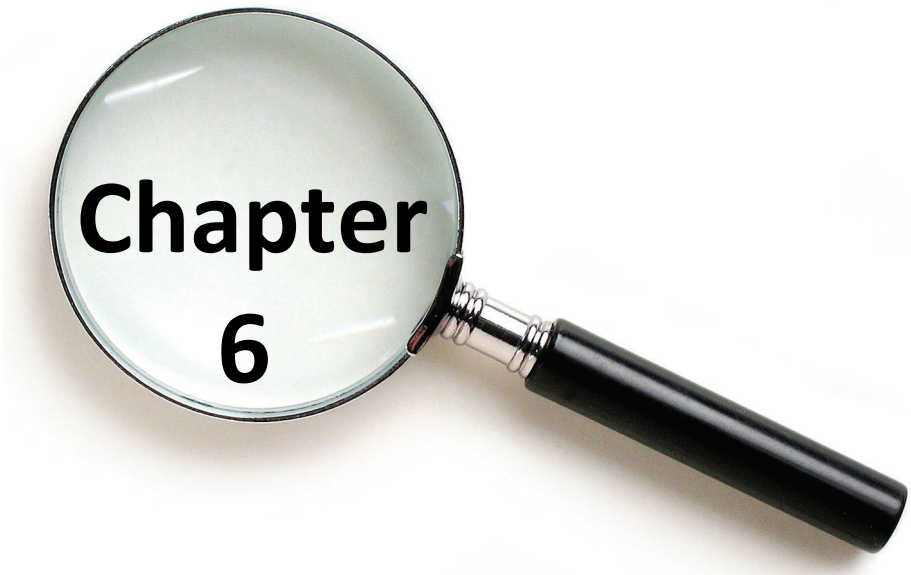

Underrepresentation of patients with pre-existing cognitive impairment in pharmaceutical trials on prophylactic or therapeutic treatments for delirium: a systematic review

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Abstract

Objective: Representation of hospitalized patients with pre-existing cognitive impairment in pharmaceutical delirium trials is important because these patients are at high risk for developing delirium. The aim of this systematic review is to investigate whether patients with cognitive impairment were included in studies on pharmacological prophylaxis or treatment of delirium and to explore the motivations for their exclusion (if they were excluded).

Study design: This study was a systematic review. A MEDLINE search was performed for publications dated from 1 January 1985 to 15 November 2012. Randomized and non-randomized controlled trials that investigated medication to prevent or treat delirium were included. The number of patients with cognitive impairment was counted, and if they were excluded, motivations were noted.

Results: The search yielded 4,293 hits, ultimately resulting in 31 studies that met the inclusion criteria. Of these, five studies explicitly mentioned the percentage of patients with cognitive impairment that were included. These patients comprised a total of 8% (n=279 patients) of the 3,476 patients included in all 31 studies. Ten studies might have included cognitively impaired patients but did not mention the exact percentage, and sixteen studies excluded all patients with cognitive impairment. The motivations for exclusion varied, but most were related to the influence of dementia on delirium.

Conclusion: The exclusion of patients with pre-existing cognitive impairment hampers the generalizability of the results of these trials and leaves clinicians with limited evidence about the pharmacological treatment of this group of vulnerable patients who have an increased risk of side effects.

Introduction

Cognitive impairment and dementia are recognized as major risk factors for delirium, especially in hospitalized patients (1;2). Studies have shown that the number of patients with Alzheimer's disease who experience delirium varies from 22% to 89% in community-based and hospitalized populations (3). After experiencing delirium, patients with pre-existing cognitive impairment can experience a significant decline in both functional and cognitive abilities (4;5) that affects self-maintenance and independent living. Therefore, pharmacological interventions that aim to prevent or decrease the severity of delirium symptoms are important for preventing the sequelae of delirium.

For practical and statistical reasons, pharmacological trials often only include patients who are relatively healthy. However, the patients who will actually use the medications in daily life may differ in important ways (6). Patients with pre-existing cognitive impairment represent a large portion of the patients with delirium, but it is unknown if they are indeed included in pharmacological delirium research. In patients with cognitive impairment, underlying pathophysiological mechanisms, such as imbalances in various neurotransmitter systems or the effects of inflammation on the brain via cytokines, may differ between patients with and without neurodegeneration. These differences may also cause variations in the effects and side effects of medications (7;8). Also, frequently, studies do not include a clear statement explaining why older patients with multimorbidity were not included (9).

Therefore, the aim of this systematic review was to investigate whether patients with pre-existing cognitive impairment were included in studies on the pharmacological prophylaxis or treatment of delirium and the motivations for their exclusion if they were excluded.

Methods

Search strategy

We conducted a systematic search of the literature published from 1 January 1985 to 15 November 2012 in MEDLINE. We used a search strategy developed by the Cochrane Dementia and Cognitive Improvement Group and combined this strategy with the search strategy used for the 2010 National Institute for Health and Clinical Excellence (NICE) guideline (10). Furthermore, we checked the references of the NICE guideline. See Appendix 1 for a complete description of the search strategy.

Selection procedure

We included original studies in the English or Dutch language that included participants older than 18. No other languages were included due to possible translational problems and because we felt bias of the results would be limited as we do not intend to meta-analyze the overall treatment effect in patients with cognitive impairment. Both randomized and non-randomized controlled trials that investigated medication for the prevention and/or treatment of non-alcohol related delirium in adults were included. We

excluded studies that did not diagnose delirium by using the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Secondly, we excluded studies that did not report on incidence/prevalence, severity or duration of delirium as one of the outcome measures. See Figure 1.

Data extraction

All data were independently extracted by two investigators (EG and AJ). In addition to the study and participant characteristics, we registered whether cognitive impairment or dementia was an exclusion criterion and whether cognitively impaired patients were enrolled. If cognitively impaired patients were excluded, the authors were approached to determine their motivation for exclusion. Disagreements that arose during the data abstraction were resolved through discussion with a third investigator (BM). We discussed for instance the articles of Hu and Kim and decided that we should not include these articles as they do not full fill our inclusion criteria (11;12).

Quality assessment

To assess internal validity, all the retrieved articles were scored using the risk of bias tool developed by the Cochrane Collaboration (13). This tool includes the following items:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessments (detection bias)
5. Completeness of outcome data (attrition bias)
6. Selective outcome reporting (reporting bias)

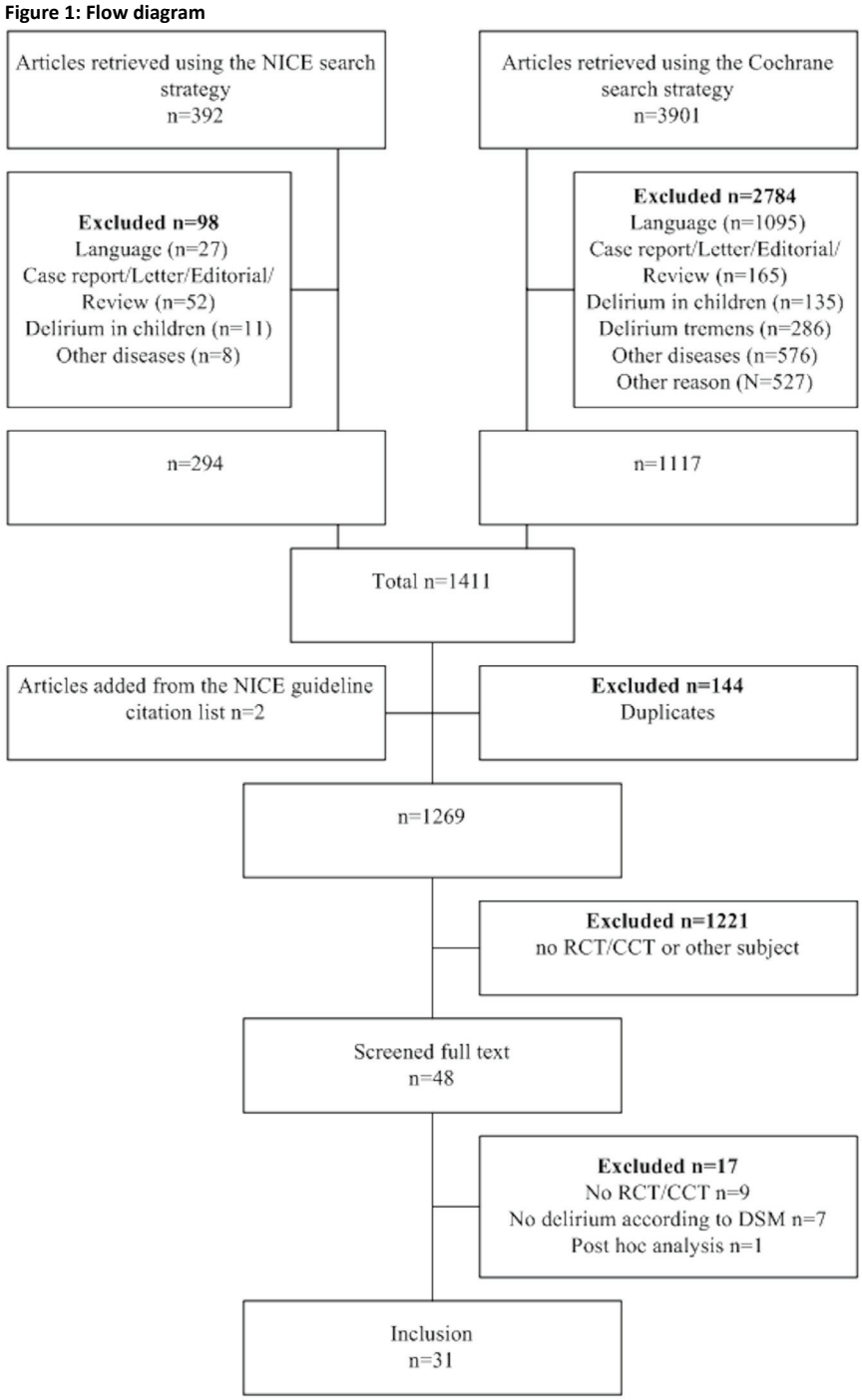
The studies could be assessed as having either a 'low risk of bias' or a 'high risk of bias' for each of these six domains. A study was considered to be of good methodological quality when it had a 'low risk of bias' for four items or more; moderate quality was defined as a 'low risk of bias' for three items; and low quality was defined as two or fewer items that received a 'low risk' rating.

Results

Search results

The combination of search terms yielded 4,293 hits. Checking the references of the Devlin review did not yield any additional studies; checking the references of the NICE guideline produced two additional studies (Figure 1). We screened the titles and the abstracts of 1269 potentially relevant papers and read the full text of 48 papers (Figure 1). The search ultimately yielded 31 studies that met the inclusion criteria (14-44).

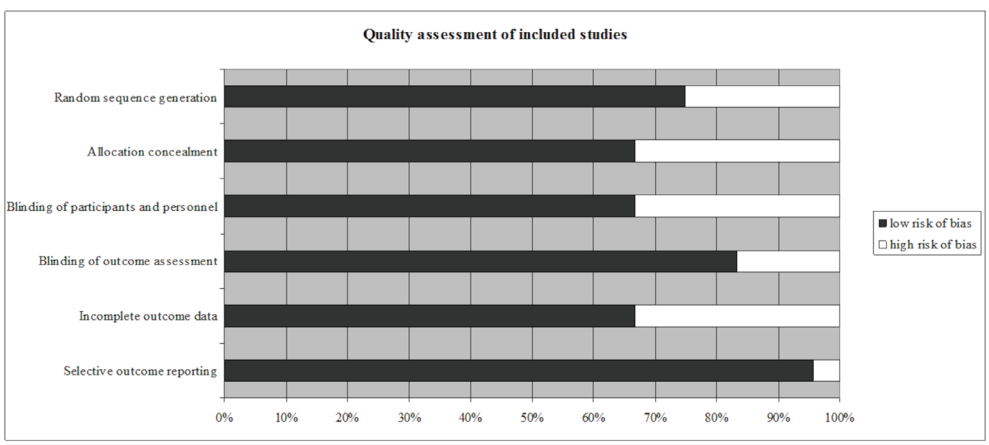
Figure 1: Flow diagram



Quality assessment

Of the 31 included studies, the majority (n=22) had good methodological quality. Three studies (27;29;41) had moderate methodological quality, and the remaining six studies had low methodological quality (19;21;33;36;42;44) (Figure 2). Seven studies did not describe the randomization process clearly (21;27;29;33;36;38;44), and one study was a controlled clinical trial (21) that had a high risk of allocation concealment and random sequence generation bias. Three studies were open-label studies (23;29;36), four studies had a single-blind design in which only the outcome assessor was blinded (23;27;31;36) and three studies (16;21;44) were not blinded. In these cases, there was a high risk of bias in the blinding of the participants and personnel and outcome assessment. Two studies failed to describe the procedure (26;42). In total, eight studies did not perform an intention-to-treat analysis, which may have introduced attrition bias (15;17;24;27;33; 35;40;42;). In most cases, all outcomes described in the methods section were reported in the results section; therefore, the risk of reporting bias was low in all of the studies except one (24).

Figure 2: Quality assessment of included studies



Characteristics of included studies

The total number of participants was n=3,467, ranging from 15 to 457 per study. The mean age of the participants ranged from 39.2 to 88.0 years. The study settings included outpatient clinics, hospital wards and intensive care units (ICUs) (see Tables 1 and 2).

Representation of patients with pre-existing cognitive impairment

Four prophylactic and one treatment study, with a total of 486 patients, reported the percentages of patients with cognitive impairment who were included. The percentages varied between 7.5 and 100 in the prophylactic studies and was 47 in the treatment study, for a total of 279 patients with cognitive impairment (see Table 1 and 2). Six prophylactic

studies and four treatment studies might have included patients with cognitive impairment; they did not specify cognitive impairment as an exclusion criterion. Nine prophylactic studies and seven treatment studies clearly excluded patients with cognitive impairment. There was no difference in methodological quality between the studies that did and did not include patients with dementia.

Motivations for not including patients with pre-existing cognitive impairment

Three studies reported the motivation for excluding patients with pre-existing cognitive impairment (35;38;40). We contacted the authors of the other thirteen articles that excluded patients with cognitive impairment, and seven responded. The reasons for excluding cognitively impaired patients (some mentioned more than one reason) were the expected legal burden (2), issues related to the study medication (2), issues related to the research design (2), and issues directly related to dementia (14). The dementia-related issues were difficulty judging treatment effect (7); interference with the treatment effect (2); the believe that these patients were not present in the eligible patient group (4); and the believe that these patients were more likely to be excluded or to decline participation (1).

Table 1a: Prophylactic RCTs included in this review that did not exclude patients with cognitive impairment (n=1,812)

Author (year)	Overall quality of study	Study population	Sample Size	Intervention	Assessment of cognitive impairment	% of patients with cognitive impairment
Al-Aama T (2011)	Good	Acute medical care patients	145	Melatonin 0.5 mg vs. placebo	Medical history	20%
Gamberini M (2009)	Good	Elective cardiac surgery patients	120	Rivastigmine 1.5 mg 3dd vs. placebo	MMSE	Not reported
Girard TD (2010)	Good	Mechanically ventilated patients	101	Haloperidol 5 mg vs. ziprasidone 40 mg vs. placebo	Medical history BDRD, IQCODE	Not reported
Kalisvaart KJ (2005)	Good	Acute or elective hip surgery patients	430	Haloperidol 0.5 mg three times daily vs. placebo	MMSE, IQCODE	Not reported
Kaneko T (1999)	Low	Elective gastrointestinal surgery patients	80	Haloperidol 5 mg iv vs. saline 0.9%	Not reported	7.5%
Kim KY (1996)	Low	Cardiac surgery ICU patients	127	Flexible dosages, usually cimetidine 900 mg iv/24 h or ranitidine 150 mg iv/24h	Not reported	Not reported
Marcantonio ER (2011)	Good	Patients undergoing hip fracture repair	16	Donepezil 5 mg vs. placebo	Medical history IQCODE	43%
Moretti R (2004) *	Low	Subcortical vascular or multi-infarct dementia patients	230	Rivastigmine 3-6 mg/day vs. cardio aspirin 100 mg/day	Medical history NINDS-AIREN, DSM-IV, MMSE	100%
Pandharipande PP (2007)	Good	Mechanically ventilated medical and surgical ICU patients	106	Sedation with dexmedetomidine vs. lorazepam	Medical history IQCODE	Not reported
Wang W (2012)	Good	Noncardiac surgery ICU patients	457	Haloperidol 0.5 mg bolus followed by 0.1 mg/hr iv vs. placebo	Medical history	Not reported

Table 1b: Prophylactic RCTs included in this review that excluded patients with cognitive impairment (n=1,083)

Author (year)	Overall quality of study	Study population	Sample Size	Intervention	Assessment of cognitive impairment	% of patients with cognitive impairment
Aizawa K (2002)	Moderate	Gastric or colon cancer laparotomy patients	40	Diazepam (0.1 mg/kg) iv bolus and a continuous infusion of flunitrazepam 0.04 mg/kg and pethidine 1 mg/kg over 8 h during the night vs. care as usual	Medical history	None
Hudetz JA (2009)	Good	Male cardiac surgery patients	58	Single dose (0.5 mg/kg, intravenous) of ketamine during anesthetic induction vs. placebo	Medical history	None
Larsen KA (2010)	Good	Elective knee or hip replacement patients	400	Olanzapine 5 mg per day vs. placebo	Medical history	None
Leung JM (2006)	Good	Spine surgery patients requiring general anesthesia	21	Gabapentin 900 mg vs. placebo	Not reported	None
Liptzin B (2005)	Good	Elective knee or hip surgery patients	80	Donepezil 5 mg vs. placebo	MMSE, CDT	None
Prakanrattana U (2007)	Good	Cardiopulmonary bypass patients	103	Risperidone 1 mg vs. placebo	Medical history	None
Sampson EL (2007)	Good	Elective total hip replacement patients	126	Donepezil 5 mg vs. placebo	MMSE	None
Shehabi Y (2009)	Good	Pump cardiac surgery patients	33	Dexmedetomidine (0.1–0.7g · kg^{-1} · ml^{-1}) vs. Morphine (10–70g · kg^{-1} · ml^{-1})	Medical history	None
Sultan SS (2010)	Low	Hip arthroplasty patients	222	Placebo vs. melatonin 5 mg vs. midazolam 7.5 mg vs. clonidine 100 umg	AMT	None

CCT = Controlled Clinical Trial. AMT= Abbreviated Mental Test, BDRS= Blessed dementia rating scale, CDT=Clock Drawing Test, DSM-IV= Diagnostic and Statistical Manual of Mental Disorders forth edition, IQCODE= Informant Questionnaire of Cognitive Dysfunction, MMSE= Mini-Mental State Examination, NINDS-AIREN= National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences.

Table 2a: Treatment RCTs included in this review that did not exclude patients with cognitive impairment (n=211)

Author (year)	Overall quality of study	Study population	Sample Size	Intervention	Assessment of cognitive impairment	% of patients with cognitive impairment
Breitbart W (1996)	Good	Adult patients with AIDS and delirium	30	Haloperidol vs. chlorpromazine vs. lorazepam at flexible dosages	Psychiatric evaluation	Not reported
Overshott R (2010)	Good	Patients with incident and prevalent delirium	15	Rivastigmine 1.5 mg once a day increasing to twice a day after 7 days vs. placebo	Medical history MMSE	47%
Reade MC (2009)	Good	Agitated delirious mechanically ventilated patients	20	0.2-0.7 mcg/kg/hour dexmedetomidine (loading dose optional) vs. haldol 0.5 to 2 mg/hour (idem)	Not reported	Not reported
Tahir TA (2010)	Good	Medical and surgical patients with delirium	42	Quetiapine flexible dosage 25-175 mg/day vs. placebo	Medical history	Not reported
Van Eijk MM (2010)	Good	ICU patients	104	Rivastigmine according to scheme vs. placebo.	IQCODE	Not reported

Table 2b: Treatment RCTs included in this review that did exclude patients with cognitive impairment (n=361)

Author (year)	Overall quality of study	Study population	Sample Size	Intervention	Assessment of cognitive impairment	% of patients with cognitive impairment
Devlin JW (2010)	Good	Intensive care unit patients	36	Quetiapine 50 mg twice daily vs. placebo	Medical history	None
Grover S (2011)	Good	Patients referred to consultation-liaison psychiatry	64	Olanzapine, risperidone and haloperidol at flexible dosages	Medical history	None
Hakim SM (2012)	Good	On-pump cardiac surgery patients	101	Risperidone 0.5 mg vs. placebo	MMSE	None
Han CS (2004)	Low	Medical and ICU patients	24	Flexible dosages of haloperidol (starting with 0.75 mg) vs. risperidone (starting with 0.5 mg) twice a day	SCID	None
Kim SW (2010)	Moderate	Hospital patients	32	Flexible dosages of risperidone vs. olanzapine	Medical history	None
Lee KU (2005)	Low	Patients referred to the psychiatric consultation service	31	Flexible dosages of amisulpride vs. quetiapine	Medical history	None
Skrobik YK (2004)	Moderate	Surgical ICU patients	73	Olanzapine (5 mg) vs. haloperidol (2.5 -5 mg) every 8 h (both starting dosages) adjusted when needed	Not reported	None

IQCODE= Informant Questionnaire of Cognitive Dysfunction, MMSE= Mini-Mental State Examination, SCID= Structured Clinical Interview according to DSM-III-R criteria.

Table 3a: Quality of prophylactic RCTs included in this review that did not exclude patients with cognitive impairment

Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data (attrition bias)	Selective outcome reporting	Overall quality
Al-Aama T (2011)	Low	Low	Low	Low	High	Low	Good
Gamberini M (2009)	Low	Low	Low	Low	High	Low	Good
Girard TD (2010)	Low	Low	Low	Low	Low	Low	Good
Kalisvaart KJ (2005)	Low	Low	Low	Low	Low	Low	Good
Kaneko T (1999)	High	High	High	High	Low	Low	Low
Kim KY (1996)	High	High	High	Low	High	Low	Low
Marcantonio ER (2011)	Low	Low	Low	Low	Low	Low	Good
Moretti R (2004)	High	High	High	High	Low	Low	Low
Pandharipande PP (2007)	Low	Low	Low	Low	Low	Low	Good
Wang W (2012)	Low	Low	Low	Low	Low	Low	Good

Table 3b: Quality of prophylactic RCTs included in this review that excluded patients with cognitive impairment

Aizawa K (2002)	High	High	High	Low	Low	Low	Moderate
Hudetz JA (2009)	Low	Low	Low	Low	Low	Low	Good
Larsen KA (2010)	Low	Low	Low	Low	High	Low	Good
Leung JM (2006)	Low	High	High	Low	Low	Low	Good
Liptzin B (2005)	High	High	Low	Low	Low	Low	Good
Prakanrattana U (2007)	Low	High	Low	Low	Low	Low	Good
Sampson EL (2007)	Low	Low	Low	Low	High	Low	Good
Shehabi Y (2009)	Low	Low	Low	Low	Low	Low	Good
Sultan SS (2010)	Low	High	High	High	High	Low	Low

High = high risk of bias, and low= low risk of bias, according to the 'risk of bias tool' developed by the Cochrane Collaboration (13).

Table 4a: Quality of treatment RCTs included in this review that did not exclude patients with cognitive impairment

Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data (attrition bias)	Selective outcome reporting	Overall quality
Breitbart W (1996)	Low	Low	Low	High	Low	Low	Good
Overshott R (2010)	Low	Low	Low	Low	Low	Low	Good
Reade MC (2009)	Low	Low	High	High	Low	Low	Good
Tahir TA (2010)	Low	Low	Low	Low	High	High	Good
van Eijk MM (2010)	Low	Low	Low	Low	Low	Low	Good

Table 4b: Quality of treatment RCTs included in this review that excluded patients with cognitive impairment

Devlin JW (2010)	Low	Low	Low	Low	Low	Low	Good
Grover S (2011)	Low	Low	Low	Low	Low	Low	Good
Hakim (2012)	Low	Low	High	Low	Low	Low	Good
Han CS (2004)	High	High	High	Low	high	Low	Low
Kim SW (2010)	High	Low	High	Low	High	Low	Moderate
Lee KU (2005)	High	High	High	High	High	Low	Low
Skrobik YK (2004)	Low	High	High	Low	Low	Low	Moderate

High = high risk of bias, and low= low risk of bias, according to the 'risk of bias tool' developed by the Cochrane Collaboration (13).

Discussion

This systematic review clearly states that only 8% (n=279) of patients who were included in prophylactic and treatment delirium trials (n=3,476) were patients with cognitive impairment or dementia.

The stated motivations for excluding patients with cognitive impairment varied and were frequently related to dementia. The researchers indicated that cognitive impairment/dementia hampered a clear assessment of the incidence, severity or resolution of delirium. Although we acknowledge that delirium and dementia share many symptoms (45), it is possible to diagnose delirium by adhering to the DSM criteria, especially for trained health care professionals, and if needed, research assessment tools can be used like the Confusion Assessment Method to distinguish delirium in patients with dementia (25;46;47). Furthermore, the researchers indicated that 'dementia interferes with the treatment effect' (i.e., the effect of the intervention for patients with a high risk of delirium might be different from the effect for low-risk patients). This is possible but excluding high-risk patients hampers the external validity of the trial results.

Another motivation was that 'these patients are not expected to be in the eligible patient group' (e.g., in the ICU). It is not possible to investigate this statement, especially because acutely admitted patients may not be fully conscious; therefore, cognitively impaired patients might have been included without the researchers' knowledge. Another researcher reported that 'these patients were more likely to be excluded or to decline participation in this study'. However, this statement is not supported by the studies that are included in this review; the fifteen studies that did include patients with cognitive impairment (or may have included them) did not report any dropouts that occurred because of cognitive impairment.

Apart form the arguments given by the researchers, we imagine that researchers do not include these patients because of potential objections of the Medical Ethical Committee. As it takes more time to approach a legal representative to obtain informed consent and this demands extra efforts from the research team this could explain also that these patients are frequently excluded.

None of the four studies that reported the percentages of patients with cognitive impairment that were included, performed a subgroup analysis for patients with cognitive impairment (the fifth study included only patients with dementia). The underrepresentation of patients with pre-existing cognitive impairment limits the external validity of these studies and thus the applicability of many trial results to delirious patients with pre-existing cognitive impairment. In the field of delirium research, many patient groups or settings are underrepresented, e.g. patients aged 85 and over or palliative care. However, it is of particular importance to include patients with pre-existing cognitive impairment in pharmaceutical trials as these patients are in the highest risk group for developing delirium and they have a high risk of pharmacological side effects. Furthermore, all studies on atypical antipsychotics, except for one, excluded patients with cognitive impairment. However, treatment with atypical antipsychotics can lead to serious cerebrovascular side effects and higher mortality, especially in patients with dementia (48;49). Therefore, the U.S. Food and Drug Administration (FDA) discourages clinicians from prescribing antipsychotics to delirious dementia patients and from using these medications prophylactically (50).

Because of the lack of evidence about the preventive effect of antipsychotics for delirium, the NICE guideline does not recommend prophylactic treatment in patients with an increased risk of delirium (10;51). In addition, the NICE guideline recommends reserving antipsychotics for treating delirium only in patients for whom verbal and non-verbal de-escalation techniques are ineffective or inappropriate. There are no recommendations specifically for patients with cognitive impairment, and it is not explicitly stated that the available evidence was not derived from the group for which the treatment will be prescribed. Thus, clinicians are left with limited evidence about pharmacological treatment for cognitively impaired patients with delirium or an increased risk for delirium.

Conclusion

This review shows that a minority of the total population of patients in clinical trials concerning the pharmacological prevention or treatment of delirium had known cognitive impairment. These findings indicate that the current evidence has limited applicability for daily clinical practice. Researchers should be more aware of the underrepresentation of patients with pre-existing cognitive impairment so that future delirium research includes this specific group. Clinicians should recognize that there is a gap in the evidence about the possible effects and side effects of medication for treating delirium, especially for vulnerable patients.

Appendix 1

The following search strategy was applied in MEDLINE:
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND (Primary Prevention[mh:noexp] OR prevent*[tw] OR reduc*[tiab] OR stop*[tiab] OR taper*[tiab] OR avoid*[tiab] OR "cut* down"[tiab])
AND (Delirium[mh:noexp] OR deliri*[tw] OR "acute confusion*"[tiab] OR "acute organic psychosyndrome"[tiab] OR "acute brain syndrome"[tiab] OR "metabolic encephalopathy"[tiab] OR "acute psycho-organic syndrome"[tiab] OR "clouded state"[tiab] OR "clouding of consciousness"[tiab] OR "exogenous psychosis"[tiab] OR "toxic psychosis"[tiab] OR "toxic confusion"[tiab] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/surgery"[Mesh] OR obnubilat*[tiab]) NOT (animals[mh:noexp] NOT humans[mh:noexp])

The search strategy of the NICE guideline:
1
deliri$.ti,ab.
2
(acute adj2 (confusion$ or "brain syndrome" or "brain failure" or "psycho-organic syndrome" or "organic psychosyndrome")).mp.
3
(terminal$ adj restless$).mp.
4
toxic confus$.mp.
5
delirium/
6
confusion/
7
or/1-6
8
*psychoses, alcoholic/ or *alcohol withdrawal delirium/
9
*substance withdrawal syndrome/
10
8 or 9
11
7 not 10

AND:

1
randomized controlled trial$.pt,sh.
2
clinical trial$.pt,sh.
3
random allocation/
4
double blind method/
5
single blind method/
6
((clin$ or control$) adj5 trial$).ti,ab.
7
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
8
placebos/
9
placebo$.ti,ab.
10
random$.ti,ab.
11
(volunteer$ or "control group" or controls or prospective$).ti,ab.
12
research design/
13
or/1-12
14
animals/ not humans/
15
13 not 14

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Estimating the time-to-benefit for preventive drugs with the Statistical Process Control method: an example with alendronate

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Submitted

Abstract

Importance: For physicians dealing with patients with limited life expectancy, knowing the time-to-benefit (TTB) of preventive medication is essential to support treatment decisions. Objective: To investigate the applicability of Statistical Process Control (SPC) charts to determine the TTB.

Design, setting and participants: We performed a post-hoc analysis of the Fracture Intervention Trial (FIT), a randomized controlled trial (RCT) that investigated the effect of alendronate vs. placebo on fracture risk in postmenopausal women (aged 55-81) with SPC. We show a new application of SPC, a statistical method that is used for monitoring processes for quality control. SPC was used to discriminate between normal variation over time in difference in number of fractures of placebo group and alendronate group and variation that was attributable to alendronate. Results are plotted in a graph that shows abnormal variation in difference in number of fractures directly.

Main Outcome Measure(s): Main outcome was the TTB, defined as moment at which the cumulative difference in number of clinical fractures continued to be above the upper control limit of the SPC chart (3 sigma). We performed a comparison with other statistical methods that calculated an early treatment effect.

Results: In the FIT study, 3,658 patients with osteoporosis (T score ≤-2.5 or ≥1 morphometric vertebral fracture) were included. For clinical fractures risk reduction was first significant by month 18, defined at six-month intervals with survival analysis. With SPC, the TTB was defined at 11 months for the total group (absolute risk reduction (ARR = 1.1%). For patients ≥70 the TTB was eight months (ARR=1.4%); for patients <70, it was 19 months (ARR=0.7%).

Conclusions: SPC is a clear and understandable graphical method to determine the TTB; graphs show clearly at which moment a difference occurs between two groups, there is no need to define a pre-specified time point. With SPC the TTB for alendronate is shorter (11 months) than with survival analysis (18 months) and the TTB is even shorter (8 months) in older women. Because the absolute effect is small at the moment there is a difference, the decision to start medication depends on patients' and doctors' preferences.

Introduction

The number of drug prescriptions in older patients is high (1), because the number of diseases increases with age. Consequently, they are prone to possible side effects of medication, due to altered pharmacodynamics and pharmacokinetics (2). Therefore, medication should only be prescribed to patients that are likely to benefit. For physicians dealing with older patients with multiple conditions it is important to take the life expectancy of the patient into account, as it is possible that patients will not live long enough to benefit from preventive medication. Therefore, knowing the time-to-benefit (TTB) supports treatment decisions. The TTB can be defined as the estimate of time needed until a treatment becomes significantly effective in a group of patients (3). Although it seems clear that it is important to take TTB into account when prescribing medication (4;5), the concept is seldom mentioned in trial results and is even more rarely calculated for the subpopulation of elderly (4;5).

Osteoporosis is highly prevalent at older age; it has been estimated to affect 55% of the United States population ≥50 years of age (6;7). There is sufficient evidence from randomized clinical trials that the current pharmacological therapies for osteoporosis are effective in preventing new fractures, in older patients as well (6).

The aim of this study was to use Statistical Process Control (SPC) to determine the TTB of alendronate on fracture risk in postmenopausal women with osteoporosis. SPC is a statistical method that is used in research for health care improvements, but not often in other branches of medicine (8). It is an innovative and easy to interpret method to identify significant variations in clinical outcomes in a range of health care settings. Furthermore, we compared the SPC method for defining the TTB with currently available methods in the literature.

Methods

Calculation of the TTB with Statistical Process Control

Original data of the FIT study

Original data of the Fracture Intervention Trial (FIT) were used to determine the TTB (9;10). The FIT study was a randomized placebo-controlled trial investigating the effect of alendronate versus placebo on the risk of morphometric vertebral fractures as well as clinically evident fractures of all sites in postmenopausal women (55-80 yr. of age). The methods are described elsewhere (9;11). The present analysis was performed in all patients (n=3,658) with confirmed osteoporosis (either a femoral-neck Bone Mineral Density (BMD) T-score ≤-2.5 (n=1,631), or at least one morphometric vertebral fracture (n=2,027)). The outcome of interest was any new clinical fracture (either clinical vertebral fracture or non-vertebral). A clinical fracture was defined as a fracture diagnosed by a physician and confirmed by written reports or radiographs. We chose the outcome clinical fractures instead of morphometric vertebral fractures; because for clinical fractures it was clear at which moment they had developed, whereas nonclinical vertebral fractures only

become visible when a radiograph is performed. The analysis was limited to the first fracture. Patients who did not complete follow-up were censored when they left the study.

Analysis: Statistical Process Control (SPC)

We assessed the longitudinal effect of alendronate on the incidence of clinical fractures in postmenopausal women with osteoporosis using Statistical Process Control (SPC) (12-14). SPC relies on statistical methods to monitor a series of measurements (process) to indicate when a structural change, i.e. not due to chance, in the measurements has occurred. When this happens it is said that the process goes from 'in control' (stable) to 'out of control' (15). Out of control is determined by analysis of the variability of the measurements over time. An important tool used in SPC to show the results is a graphical chart, called control chart, which plots the measurements (e.g. a proportion or a mean) over time and uses the observed variability of these measurements to calculate these limits of expected variation (8). Generally, these limits are three adjusted standard deviations (called sigma's) from the mean of the measurements. When measurements cross these limits then the process is `out of control,' otherwise it is stable. The limit of three sigma is chosen because SPC implicitly uses multiple tests, one for every measurement (16).

Several types of control charts are available depending on the nature of the measurement and the purpose of the study. For this study we used the XmR chart, where 'X' stands for individual measurements, and 'mR' for moving range. The XmR chart is popular for its ability to visually depict variation when only one observation exist in each time period, in our case the cumulative difference in number of fractures per month (16). This chart has a distinctive pattern marked by three reference lines. One in the center, designating the centerline (CL), which is the average value of the measurements when the process is in control. The other two reference lines are the upper and lower control limits (UCL and LCL respectively) corresponding to the boundaries beyond which the process will be considered as out of control. The UCL and LCL are three sigma away from the center line, in order to adjust for multiple testing.

For the FIT data, the cumulative difference was measured per month and in a second analysis every two weeks. We used the measurements of the first six months to calculate the control limits. This period was chosen because we hypothesized that it takes six months for the medication to become effective in improving bone strength variation within this period can be seen as physiological fluctuation not related to the pharmacological effect of bisphosphonates (17). The rate of suppression of bone resorption by bisphosphonates increases until a limit has been reached after about three months; thereafter it remains at a constant level. Paradoxically, bone formation decreases too after starting with bisphosphonates as a result of the coupling of bone formation and resorption in basic molecular units. Biochemical markers have shown that the decrease in

bone formation is lower and lags behind that of the suppression (18). Eventually, a balance between formation and suppression is reached in three to six months (19).
There are several rules that indicate when a relevant variation has occurred on a process control chart. Most of them are designed to identify a trend in effect rather than an absolute effect (16). Because we were interested in a sustained effect of time (the TTB), we limited the SPC analysis to one rule: the process being out of control at one point beyond three sigma as the next points also remain beyond three sigma. Thus, a successful intervention causes the process to go 'out of control' in the direction of improvement. The TTB, the estimate of time needed until a treatment and a placebo group start to differ in effect, was in this study defined as the first month at which the cumulative difference in percentages of any clinical fracture between the two study arms continued to be above three sigma.

Subgroup analysis
Because the incidence of fractures increases with age (20), older patients in trials are likely to have an increased risk of fractures compared to younger patients. Therefore we hypothesized that older patients might have a shorter TTB than younger patients. We performed pre-defined subgroup analyses for age groups (below and over 70 years and for the group of women with a T score of -2.5 or less (n=2,715).

Literature search
To compare the SPC method with other methods currently used for defining the time to effect, we searched MEDLINE with an extensive search strategy to identify randomized controlled trials (RCTs), pooled data analyses and post hoc analyses that investigated the efficacy of pharmacological treatment for clinical osteoporotic fractures in postmenopausal women. Furthermore, we included studies from a recently published overview of time to onset of efficacy in fracture reduction with current anti-osteoporosis treatments (21). We selected studies that did an analysis before the end of follow-up (within one year) to find out at which moment the outcome in the intervention and placebo group start to differ significantly.

Results

Patient characteristics
In the FIT study, 3,658 patients with osteoporosis were included, 1,841 in the alendronate group and 1,817 in the placebo group (Table 1). During the study period, there were 511 primary fractures; 190 patients had two or more reported fractures. 76 patients died, of which 20 had a fracture.

Table 1: Characteristics of the participants of the FIT study, postmenopausal women (n=3,658) aged 55-80 year with confirmed osteoporosis (either a femoral-neck Bone Mineral Density (BMD) T-score ≤-2.5 (n=1,631), or at least one morphometric vertebral fracture (n=2,027)). in this table, also the main outcome was reported.

	Alendronate group (n=1,841)	Placebo (n=1,817)	p-value
Age in years, mean (SD)	69.3 (6.0)	69.5 (5.9)	
Clinical fracture after 45 years, n (%)	935 (51%)	907 (49%)	
T-score Femoral neck	-2.74 (0.55)	-2.76 (0.55)	
Clinical fractures during follow up (36 months), n (%)	215 (12%)	296 (16%)	<0.001
Death during follow up, n (%)	40 (2%)	36 (2%)	0.69

Statistical process control

SPC analysis of the total group showed that the process went out of control after 11 months (Figure 1), when the absolute cumulative risk reduction was 1.1%. For patients aged 70 years and older (n=1,870) the TTB is shorter (after eight months, ARR = 1.4%) than for younger patients (after 19 months, ARR = 0.7%) (Figure 2a and 2b). The results were similar when two measure points per months were used (data not shown).

We also did subgroup analysis for the group with a femoral neck T score below -2.5 (n=2,715). For this group of patients, the TTB could be set at 11 months, with an absolute risk reduction of 0.5% (Figure 3). The figure shows a dip during month three to nine, therefore we checked if there was an unbalanced randomization in this subgroup. This was not the case; both groups were comparative with regard to mean age, sex, mean T-score and number of falls in the past.

Figure 1: Statistical Process Control Chart of the cumulative absolute risk reduction (ARR) in clinical fractures for the total group of patients included in the FIT study (n=3,658). Arrow at 11 months, the time-to-benefit, i.e. the first point the difference is above the upper control limit (ARR = 1.1%).

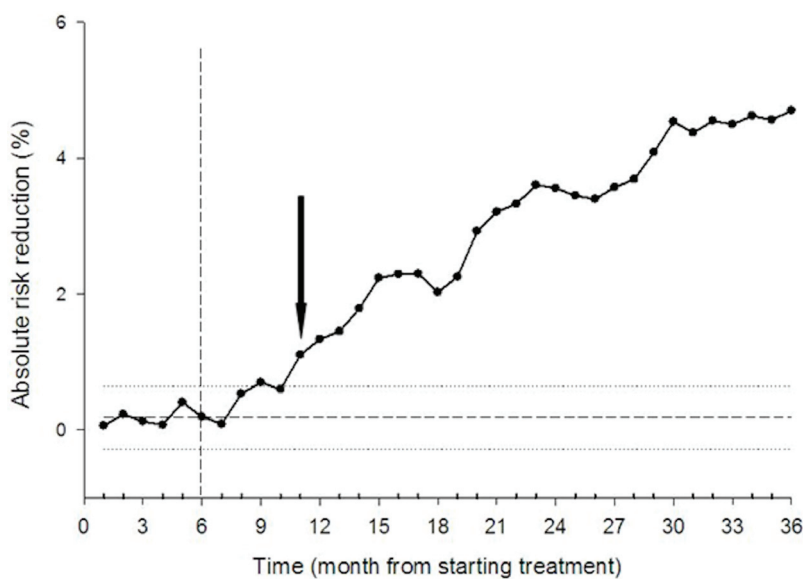


Figure 2a: Statistical Process Control chart of the cumulative absolute risk reduction (ARR) in clinical fractures for patients aged 70 years and above (n=1,870). Arrow at eight months where the process is out of control, i.e. the first point the difference is above the upper control limit (ARR= 1.4%).

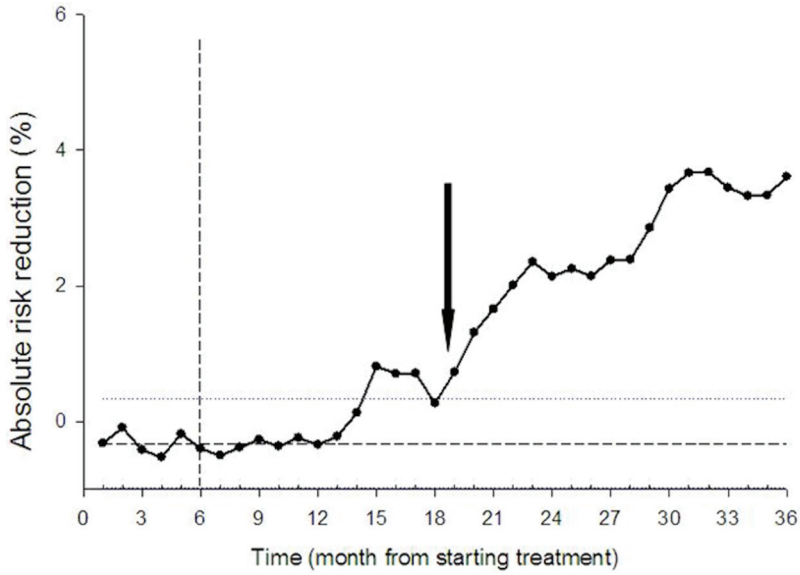


Figure 2b: Statistical Process Control chart of the cumulative absolute risk reduction (ARR) in clinical fractures for patients aged below 70 (n=1,788). Arrow is at 19 months, the time-to-benefit, i.e. the first point the difference is above the upper control limit (ARR =0.7%).

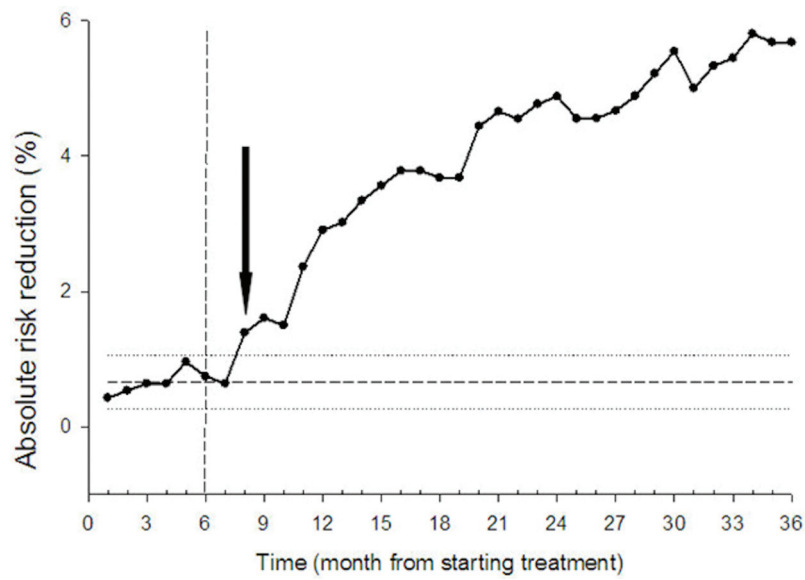
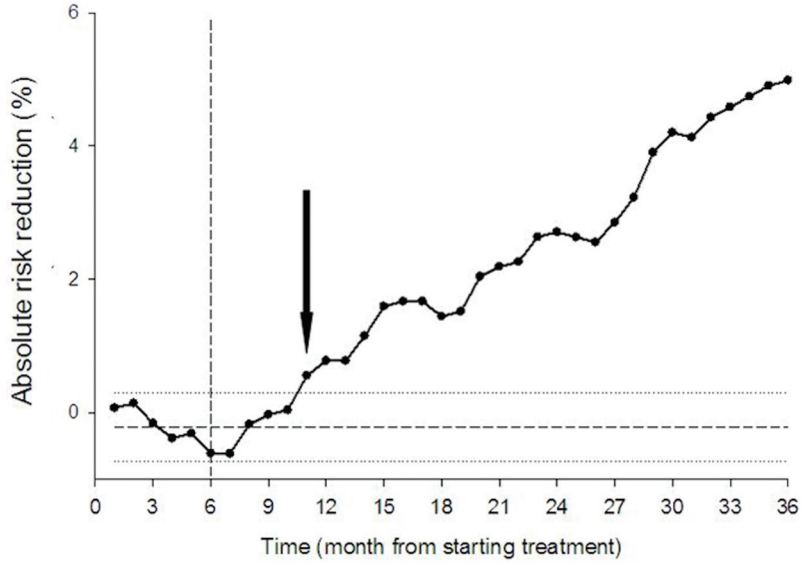


Figure 3: Statistical Process Control chart of the cumulative absolute risk reduction (ARR) in clinical fractures for patients with a femoral neck T score below -2.5 (n=2,715). Arrow at 11 months, the first point the difference is above the upper control limit (ARR=0.5%).



Literature search

The search yielded 325 articles, of which 25 were selected. Two other references (22;23) were added from the study of Inderjeeth (21). None of the identified studies mentioned the term TTB, but five studies reported the outcome before the end of follow-up, within one year (4;5;10;24;25) (Table 2).

In the original publication about the FIT study (10) the interaction between study time and treatment effect was determined with survival analysis. The reduction in risk due to bisphosphonates was significant for any clinical fracture by month 18. In another study, alendronate was effective for multiple vertebral fractures at three months already (22). In three studies survival analysis was used to determine an early effect (4;5;24). In all these cases a predefined point was used to perform a log rank test (Table 2). Adachi et al. performed a meta-analysis of individual patient data of five RCTs with 3,331 women treated with risedronate 2.5 mg or 5 mg daily (5). The outcome of interest was a new vertebral fracture. In this study a Cox regression model was used to quantify the treatment effects, with adjustment for study and number of prevalent fractures. Clinical vertebral fractures were significantly reduced in the risedronate five mg group compared with placebo in the first six months ($p<0.001$). Harrington et al. also pooled RCTs investigating risedronate vs. placebo and investigated the effect on new osteoporosis-related non-vertebral fractures. With the Kaplan Meier method the incidence of fractures at three months intervals was determined; a log rank test was used to test the treatment effect. Significance was achieved at six months (24). This was also the case for the effect of

risedronate on clinical vertebral fractures (23). Lindsay et al. published a RCT on teriparatide in which the outcome was calculated as a hazard ratio per month (4). The time to first non-vertebral fragility fracture or new or worsening back pain following treatment initiation was analyzed using Cox partial likelihood regression treating time on therapy as a linear, time-dependent covariate. In this model the study period was split up in three time intervals (0-7 months, 7-14 months, >14 months). This model assumes that the hazard remains constant during these time periods. Qu et al. performed a post hoc analysis three and six months of a RCT on raloxifene enrolling 6828 women (25). Significance was reached at three months for clinical vertebral fractures. In all four studies, the absolute effect was small.

Table 2: Randomized controlled trials and post hoc analyses of the pharmacological treatment of osteoporosis in postmenopausal women that reported an analysis at interim moments (within one year)

Publication/ Study name	Intervention	Statistical method	Outcome	Follow-up (years)	Outcome significant <1 year
Adachi 2005 (pooled data VERT trials) (5)	Risedronate 5 mg (n=1,118) vs. risedronate 2.5 mg (n=1,112)	Cox regression model at 6-months intervals	Clinical vertebral fractures	1.5 to 3	Yes
Black 2000 (FIT, clinical and vertebral fracture arm) (10)	Alendronate 5-10 mg (n=1,841) vs. placebo (n=1,817)	Survival analysis at 6-month intervals	Clinical vertebral fractures	4	No
Harrington 2004 (pooled data VERT trial) (24)	Risedronate 5 mg (n=564) vs. placebo (n=608)	Survival analysis at 6-month intervals	Non vertebral fractures	3	Yes
Levis 2002 (data from FIT study) (22)	Alendronate (n=1,005) vs. placebo (n=1,022)	Survival analysis at 6-month intervals	Multiple systematic fractures	3	Yes
Lindsay 2009 (post hoc) (4)	Teriparatide 20 mcg (n=541) vs. teriparatide 40 mcg (n=552) vs. placebo (n=544)	Defining hazard ratio per month; three time intervals (0-7 months, 7-14 months, >14 months)	Non vertebral fractures or worsening of back pain	2	Yes
Qu 2005 (MORE, post hoc) (25)	Raloxifene (n=5,129) vs. placebo (n=2,576)	Post hoc analysis at 3 and 6 months (relative risk)	Clinical vertebral fractures	3	Yes
Roux 2004 (VERT) (23)	Risedronate 5 mg (n=1,016) vs. placebo (n=1,022)	Survival analysis at 3-month intervals	Clinical vertebral fractures	3	Yes

Discussion

SPC is a graphical method with a clear and understandable chart for calculating the TTB on data of a randomized controlled trial. With this method, we defined that the TTB of alendronate for the prevention of osteoporotic clinical fractures was 11 months in this population of postmenopausal women with osteoporosis. Although much literature on osteoporosis therapy is available, few authors report an analysis before the end of follow

up and even less report a time-to-event analysis for clinical fractures. Most frequently, a survival analysis was used at specific large time intervals (table 2). In the original FIT-study, an early effect of alendronate was determined by using survival analysis at 6-month intervals; for clinical fractures the reduction in risk was first significant for any clinical fracture by month 18 with an absolute risk reduction of 2% (10). The advantage of SPC in comparison with survival analysis is that the measure point at which the difference is above three sigma is directly visible in the graph and therefore can be detected at a glance, while in survival analysis multiple analyses have to be done.

The reported absolute risk reductions are small. The TTB is dependent on the a priori chance in a population of developing an osteoporotic fracture. The clinical decision to start a treatment depends on patient's and physician's preferences and the patient's clinical condition (26). By knowing the TTB a treatment can be better adjusted to patients with limited life expectancy, although estimating this has proven to be difficult (27). The SPC graph could also be presented as number needed to treat (NNT=1/ARR) over time. Combining a patient's life expectancy with the NNT at that moment, could help in clinical decision making both for the patient as for the clinician (28).

Because the TTB is dependent on the a priori chance of having a (vertebral) fracture, and the chance for a (vertebral) fracture is higher for patients above 80, than for the subgroup of patients above 70 included in the FIT study (29), it can be assumed that the TTB for alendronate may be even shorter in an older geriatric population with high risk of falling and fractures. As a result, we conclude that withholding bisphosphonates in older patients with a life expectancy of more than eight months is not evidence-based clinical practice, when reducing risk of additional fractures is the patient preferred clinical goal. Fractures are associated with significant mortality and morbidity and represent a substantial economic burden to society (30).

SPC is a statistical method that was originally designed for quality control to monitor and control a process; it provides a signal when abnormal variation in the process is detected. There are several rules that indicate when a process is out of control. Apart from the rule we have used to indicate that the process is out of control, i.e. one point being above three sigma, there are frequently used rules that are able to detect a trend over time. If we would have used these trend rules, we would have found an earlier effect. Using SPC in this way could help in defining the time period any effect is lacking for certain. However, this early effect would correspond with a very small absolute effect which might not be clinically relevant. In cohort studies one could think of many alternative ways to use SPC, for example to measure treatment and side effects over time.

A limitation of applying SPC for defining the TTB is that when the first measurements in the study reflect an unstable process, it is impossible to define the upper and lower limits. If an early effect of treatment is expected one should find an alternative way to define the central line and its limits, for example by using different time intervals between measurements, or preferably by using data before the start of the treatment.

Conclusion

Statistical Process Control is a novel method to define the TTB for medication used to treat and prevent clinical outcomes. Its main advantage is that it becomes clear at a glance when the effect occurs. We would encourage scientists to report the TTB, especially in studies for preventive medication in older patients. Clinical decision-making can be made more evidence-based by applying the TTB and the absolute risk reduction so that the pros and cons of initiating or stopping medication can be weighed for an individual patient with limited life expectancy.

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Reviews of individual patient data are useful for geriatrics: an overview of available IPD-reviews

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Abstract

Objectives: To determine how many IPD reviews that included older people were available in MEDLINE, as well as whether the effectiveness of treatments differed between older and younger patients.

Design: An overview of IPD reviews

Setting: A MEDLINE search was conducted for IPD reviews of randomized controlled trials published before July 2012.

Participants: IPD reviews that either presented a regressionmodel that included age as a factor or a subgroup analysis of patients aged 70 years and above, or IPD reviews of which all participants were aged 70 years and above.

Measurements: We evaluated whether the IPD reviews reported similar conclusions for both the younger and older populations.

Results: 26 IPD reviews with a subgroup of older individuals, as well as eight reviews with only older individuals, were included (median n=3,351). The most important reason for choosing an IPD review was the ability to perform a subgroup analysis in the older population. 14 IPD reviews suggested that older people should receive distinct treatments compared to younger people due to differences in effectiveness, of which six reviews indicated that the investigated treatment(s) should be avoided in older patients.

Conclusion: IPD review is a valuable approach for generating evidence in older patients. The treatment effects frequently differed between older and younger patients. Still, the application of IPD results to geriatric patients should be done cautiously, as they are often excluded from primary trials. The collaborative sharing of raw data should be promoted to improve evidence-based decisions for this group.

Introduction

The currently available evidence of therapeutic interventions from randomized controlled trials (RCTs) is often based on studies conducted in otherwise relatively healthy adults, and the numbers of older patients enrolled in these trials are often insufficient to perform meaningful subgroup analyses. Available evidence cannot be directly applied to the geriatric patient, given that the treatment responses and side effects of drugs can be different due to altered pharmacodynamics and pharmacokinetics (1). Furthermore, older patients often present with more than one disease or geriatric syndrome with the risk of interactions of treatments, and the outcomes of interest in geriatric medicine may preferentially emphasize patient-centered outcomes, such as quality of life, mobility and functional status, rather than the conventional disease-specific outcomes. Finally, the timing of outcome events is a critical issue in older patients given their more limited life expectancy.

Therefore, it is important to generate evidence focused specifically on geriatric patients. The highest level of evidence, and thus the golden standard, is provided by a review of individual patient data (IPD) (2;3). An IPD review involves the central collection, validation, and if possible a reanalysis (IPD meta-analysis) of 'raw' data from all clinical trials that have addressed a common research question (2). With this method, obtaining information about older patients is possible by combining the sparsely included older patients from the individual trials. This promising approach will generate high quality evidence targeted at geriatric patients. Recently, we commented on a methodological report as an example of a review for which an IPD review might have been beneficial (4).

Using the original study data offers the possibility to analyze any subgroup of interest by redefining subgroup membership (5;6). Examining subgroups in traditional (non-IPD) reviews suffers from numerous shortcomings. First, individual trials frequently do not report subgroup effects (i.e. stratified results) that are required in a traditional meta-analysis. Although there is the option to use the mean (median) age of each study as a covariate in the meta-analysis, such an approach yields very limited power (7). Furthermore, if trials do report on subgroups by age, they often rely on different cut-offs for defining subgroups, which hampers their pooling in traditional reviews. In addition, potential confounders are inconsistently reported in the original studies (5;6). With IPD review, it is possible to compare studies that employed different instruments to obtain comparable outcomes by redefining variables, which is especially relevant for patient-centered outcomes, such as quality of life and functionality (4). Finally, outcomes of interest are often analyzed at specific moments in time that differ across studies, whereas an IPD review can report data representative of any time point (3;9). This offers the possibility of more precisely estimating the time to treatment effect for a given group, which is of the utmost importance in the older patient with a limited life expectancy. However, performing IPD reviews is more time-consuming and costly than using aggregated data reported in publications. The original authors must be willing to share the data, the recoding of data takes time and additional statistical expertise is needed.

In the last 20 years, the publication of IPD reviews has increased (3). Whether this method is also used to enlarge the body of relevant evidence for the older population is unknown. The objective of this study was to investigate the inclusion of older populations in IPD reviews available through MEDLINE. Additionally, we investigated whether the treatment outcomes differed between the older and younger patients.

Methods

Search strategy

We performed a systematic search in MEDLINE (which includes all reviews published in the Cochrane Database of Systematic Reviews) to identify relevant IPD meta-analyses and systematic reviews published before July 2012. The search strategy was based on those used in two previous reviews (3;8). It consisted of the identification of randomized trials, a sensitive search to identify meta-analyses and systematic reviews, as well as a specific search to identify papers concerned with individual patient data. These three search methods were combined to provide a sensitive search for IPD reviews of RCTs.

Review Selection

Three authors (EG, BM and HR) independently selected potential IPD reviews based on titles and abstracts. We included reviews of individual patient data derived from several RCTs. Inclusion required that either a regressions model that included age as a factor was performed or a subgroup analysis was performed in patients of 70 years of age and above, or that all participants were 70 years of age or older.

Data Extraction

A standardized data extraction form was used to collect the following data from the full-text articles: number of RCTs from which data were obtained, number of patients in the original studies, mean ages of patients, if stratification for age was used, number of older patients on which subgroup analyses was performed, mean ages of subgroups, aims of studies, outcomes and differences in outcomes between the total groups of patients and related subgroups, as reported in the conclusions by the original authors. The conclusions of the reviews that included subgroups of older patients were categorized to determine whether the investigated treatments exhibited identical, different, improved or diminished results in the older age groups compared to the younger groups. Furthermore, we evaluated whether the outcomes in the oldest group were comparable with those of the younger group based on reports of p-values, relative effect measures (i.e., relative risk, odds ratio or hazard ratio) or absolute differences in effect. For the reviews that included only older patients, the rationale for choosing an IPD review, instead of a traditional systematic review, was identified.

Applied IPD Methodology

To our knowledge, no tools for assessing the methodological quality of IPD reviews are currently available. As a result, we screened the included IPD reviews on several items mentioned in an earlier study (6). First, we described the rationale for performing an IPD review rather than a traditional review. Second, we determined how many authors were asked to share their data compared to how many actually provided data. In addition, we investigated whether the studies with available data differed with respect to results and outcomes from studies for which data were not available, given that these differences can introduce selection bias. Third, we determined whether the researchers had used the one- or two-stage method. In the two-stage method, the results are first calculated separately within each study. In the second step, the outcome measure of interest (e.g., odds ratio, relative risk) from each individual study is then combined using traditional meta-analytical techniques taking into account the precision by which the outcome measure has been measured in each study. With the one-stage method, all patient data from all studies are simultaneously entered into a single database, taking into account the fact that patients within a study are more similar than patients originating from different studies. In the one-stage approach, the impact of patient-level covariates (e.g., age, presence of comorbidity) and study-level covariates (e.g., blinding for outcome assessment applied, differences in treatment protocol) can be simultaneously examined (3,9).

Results

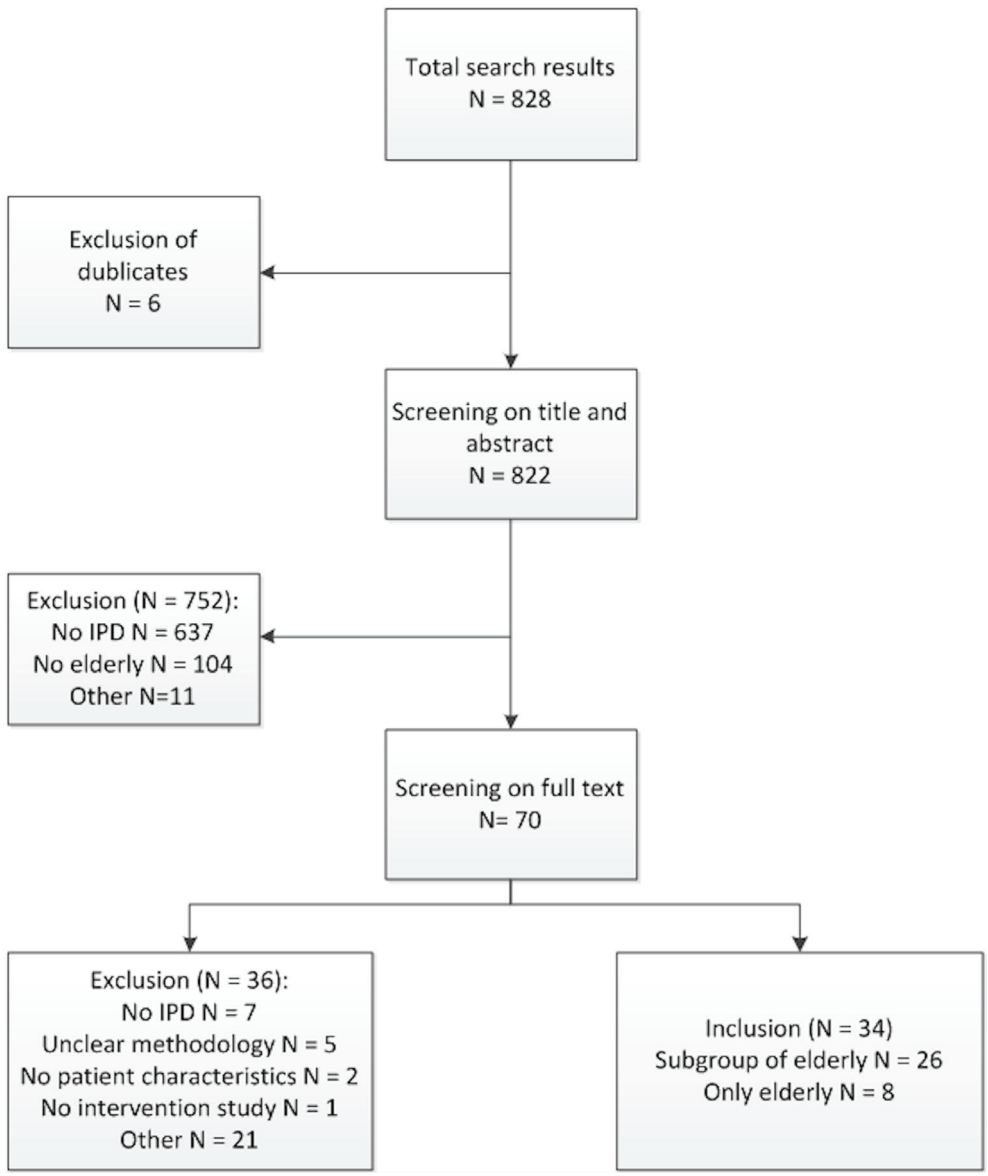
Identifications of studies

The search strategy yielded 828 papers (Figure 1). Of those, 637 were not classified as IPD reviews, and 104 did not contain a subgroup analysis of older patients. The full text of the remaining 70 studies was screened. Of these, 26 were IPD reviews that included a subgroup of older patients, and eight were IPD reviews that included only older patients (>70 years). Thirty-six studies were excluded after screening the full text for several reasons (Figure 1). Therefore, the final number of IPD reviews with an interest in elderly patients included in our overview was 34.

Study characteristics

We included eight IPD reviews pertaining only to older patients, as well as 26 IPD reviews with subgroups of older patients or age as a factor in the regression model. In 10 cases, stratification for age was used. The total sample sizes of the included IPD reviews ranged from 65 to 68,517 (Median n=3,315). Most of these reviews considered an oncologic al (n=10) or cardiologic topic (n=8). Data on baseline characteristics considered important for the geriatric population, such as functionality or living circumstances, were reported in only three articles (10-12). Only one article reported on these factors during post-treatment follow-up, as well (11). A summary of the main characteristics of the 34 IPD reviews can be found in table 1 (online appendix).

Figure 1: Flowchart



Applied IPD Review Methodology

The most frequently reported reasons for choosing an IPD review rather than a traditional review was the ability to perform a subgroup analysis for age, as well as a subgroup analysis with patient characteristics other than age (e.g., different tumor parameters or type of drug) (Table 2) (13,14).

The one-stage method was used in 26 cases, whereas five cases used the two-stage method and in three articles, the methods remained unclear. To compare younger and older age groups Cox regression analysis was used in ten studies, linear regression in two, logistic regression in one study and the Fisher's exact test in two studies; in the other studies the statistical method used was unclear. In eight cases, no authors were approached because the IPD review was a pre-planned pooled analysis of trials. In ten cases, the data were already available in a large database. In five articles, it was unclear whether the authors were approached. In 11 cases, the original authors were asked to share their data. The number of authors that were approached ranged from three to 40. Overall, 87% of the potential studies were included in the IPD review. Differences between the studies for which authors did or did not provide data were unclear in all the related articles. The potential impact of missing data was described in only four articles.

Table 2a: Reasons for choosing IPD for reviews with a subgroup of older patients (n=26)*

Subgroup analysis for age or regression model with age as a factor (n=22)
Complications following pacemaker implantation (18)
Stenting vs. endarterectomy for symptomatic carotid stenosis (31)
Cytoreductive surgery for endometrial carcinoma (32)
Early aspirin in acute stroke(22)
Epidermal growth factor receptor inhibitors for head and neck carcinoma (12)
Primary percutaneous coronary intervention (19)
Influence of participants'characteristics on anti-fracture efficacy of vitamin D (33)
Radiotherapy for ductal carcinoma in situ of the breast (15)
Tamoxifen for breast cancer (34)
Early supported discharge services for stroke patients (11)
Selective serotonin reuptake inhibitors and venlafaxine for depression (35)
Blood glucose monitoring in type 2 diabetes mellitus (36)
ACE inhibitors for patients with heart failure (37)
Premix or basal insulin for type 2 diabetes melltiusn(21)
Cisplatin-based chemotherapy for patients with non-small-cell lung cancer (38)
The implantable defibrillator for ventricular arrhytmias (17)
CABG vs. PCI for multivessel coronary artery disease (20)
Early revascularization for patients with cardiogenic shock due to acute coronary syndrome (23)
Risk factors for delayed healing of diabetic foot ulcers (39)
Recurrence rates after abdominal surgery for complete rectal prolapse (40)
Chemotherapy for resected colon cancer (24)
Palliative chemotherapy for advanced colorectal cancer (10)
Follow-up longer than original trials (n=1)
Effect of daily aspirin on long-term risk of death due to cancer (41)
Time-to-event analysis (n=3)
20 year follow-up after radiotherapy in breast cancer (42)
Routine vs selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome (16)
Interferone for multiple myeloma (43)

* The references of table 2a and 2b can be found in the appendix

Table 2b: Reasons for choosing IPD for reviews that included only older patients (n=8)

Subgroup analysis for age or regression model with age as a factor
Gastrointestinal tolerability of NSAIDs (44)
Subgroup analysis other than age (n =3)
Thalidomide addition in treatment for multiple myeloma (13) Effect of donepezil in older vs. newer trials (14) Graduated compression stocking thromboprophylaxis for elderly inpatients (45)
More information needed about patient characteristics (n=1)
Additional exercise during hospitalization (46)
Time-to-event analysis (n=1)
Long-term effects of stress for systemic hypertension (47)
IPD is considered the gold standard (n=1)
Effect of donepezil on functionality (48)
Unclear (n=1)
Donepezil vs. placebo in Alzheimer dementia (49)

Comparisons of Younger and Older Populations

In the 26 IPD reviews that compared older and younger populations, four types of conclusions were drawn by the authors (Figure 2). In five cases (19%), the analysis of individual patient data showed that the investigated treatment was more effective in the older patients than in a younger population; e.g., radiotherapy for ductal carcinoma in situ (15) and routine invasive strategy in non-ST segment elevation acute coronary syndrome (16) showed superior results in older patients. In only one study this was not new knowledge but confirmation of what was found previously in small cohort studies that were suspect for bias according to the authors (17). On the other hand, five IPD analyses (19%) indicated that the investigated treatment had less effect in the older patients compared to younger patients, or that the elderly patients had more complications. For instance, this was the case with complications after pacemaker implantation (18) and mortality after percutaneous coronary interventions (19). Here also one study confirmed already known relationships (20).

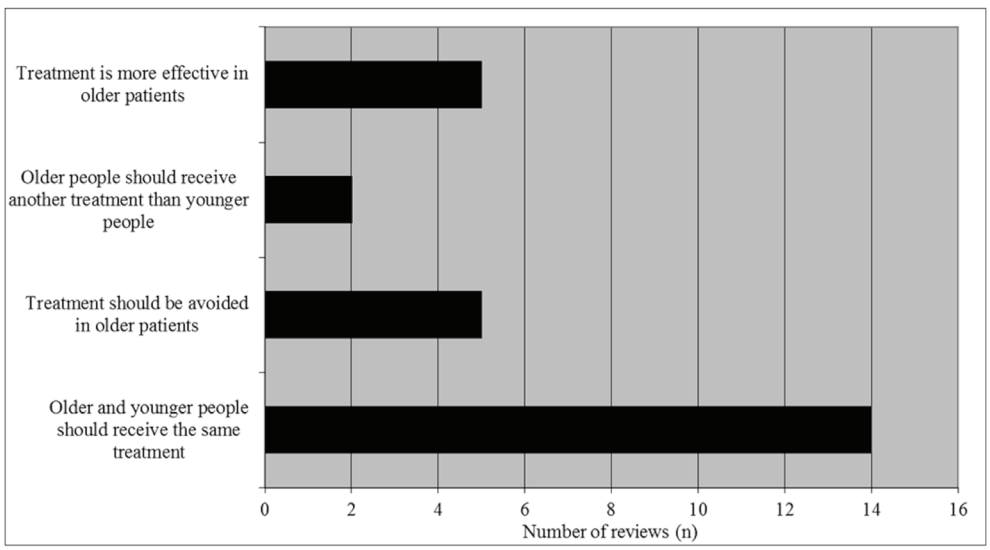
Two reviews (8%) suggested that a different treatment is recommended in the older subgroup. A different type of insulin was recommended in older type 2 diabetes mellitus patients (21), and coronary artery bypass is preferred above percutaneous coronary intervention in multivessel disease (20). In the latter the conclusion regarding age was already described before, but in combination with other subgroup analysis new knowledge was extracted.

Finally, 14 reviews (54%) reported no difference in the effects and complications of the investigated treatments between the younger and elder populations. For example, early aspirin use in stroke produced the same results across different age groups (22), early revascularization in cardiogenic shock was beneficial for all subgroups (23) and adjuvant chemotherapy in resected colon cancer exhibited comparable results among different age groups (24).

Most of the 26 reviews (n=17) reported the outcomes in older and younger patients on an absolute scale rather than only presenting a relative measure of effect. Two articles

addressed only the benefits and believed exploring harms was beyond their scope, the other 24 studies examined both the benefits and harms by age.

Figure 2: Conclusions of the 26 Individual Patient Data (IPD) reviews that included only older people



Discussion

26 IPD reviews published prior to July 2012 were available through MEDLINE (including all Cochrane reviews) that provided reports for subgroups of older people, and eight were available that reported exclusively on an older population. Of the 26 reviews, 12 (46%) provided evidence for different treatment effects between older and younger patients; of those, nine provided new information. This observation confirms that information retrieved from studies with a majority of younger, healthier patients cannot necessarily be directly extrapolated to older individuals. On the other hand, the finding that the results for older patients were similar to those of younger patients is also clinically relevant because older patients are frequently undertreated (25). The main reason cited for performing an IPD-review instead of a traditional review was the greater flexibility and validity to examine whether age modifies the size of the effect of an intervention. In 26 of 34 IPD reviews the one stage approach was used: this method is recommended because it uses a more exact statistical approach and accounts for parameter correlation. It is important to specify in the protocol which method will be used, because both can provide different parameter estimates and conclusions (26). In 10 cases, stratification for age was used; this is important as treatment effect may vary across broad range of ages that are labelled as elderly (27).

Our findings confirm that IPD reviews offer additional benefit to performing primary research in older patients, which has proven to be difficult due to various reasons, such as incapability of adhering to research protocols, problems with recalling information and inability to provide legal informed consent (28-30). As a result, the number of older patients included in RCTs is generally low. IPD review offers the possibility of pooling the data of sparsely included older patients in trials, as well as combining studies that used different instruments or cut-offs for the intervention by redefining the original variables. For diagnostic studies or prognostic modeling, IPD reviews could offer the same advantages, given that the sensitivity and specificity of questionnaires and tools could differ between the older and younger populations.

The number of identified IPD reviews concerning the elderly seems to be quite low, especially in the light of the estimated IPD review publication rate of twenty per year (3). A possible explanation might be the lack of familiarity with this approach and the earlier mentioned challenges concerning performing an IPD review (4).

There are some precautions to consider when interpreting the results of the included IPD reviews. A literature search was performed in only ten of the 26 included reviews, whereas the others were based on studies that were already available in a database. This implies a risk of bias, as it is possible that only studies with positive findings were included in these IPD reviews. Although in the majority of studies (n=17) the outcomes were reported as absolute differences, there are a few (n=7) that reported the results in terms of relative risk. Identical odds ratios or risk ratios for the younger and older groups do not automatically imply that the differences in absolute risk will be similar. It is likely that older individuals have a higher background risk, and therefore the absolute difference in risk will be elevated even if the relative effect of the measure stays the same. In relation to decision making for treatments, the absolute differences in risks should be used, as they are more informative. Furthermore, extrapolating the results of these IPD reviews to the geriatric population with co-morbidities warrants caution because baseline characteristics, such as the number of co-morbidities and cognitive performance, were often missing. Additionally, performing an IPD review will not create evidence for those older individuals who are often excluded in the original trials. Finally, the reviews infrequently made use of patient-centered outcome variables that were present in three studies, and these measures may be of more relevance for older patients, compared to the disease-specific outcome measures.

Conclusion

In this study, we have demonstrated that IPD review is a valuable approach for generating evidence for older patients. In the majority of the included IPD reviews, treatment effects differed between older and younger patients. The collaborative sharing of raw data should be promoted to facilitate performing IPD reviews. Thereby, we can come one step closer to achieving evidence-based medicine in diagnostic and therapy decisions in the growing population of older and more vulnerable patients in our society.

Appendix: Table 1

Table 1a: Summary of the 26 IPD reviews that included a subgroup of older patients

Reference	No. of trials (n)	Total sample size (n)	Mean age year)	Authors' conclusions	Difference with younger/ total group	Categories for conclusion[q]	Absolute or relative risk[r]	Reason for IPD[s]
Armaganijan 2012	3	4,814	76	Older patients (>=75 years of age) are at increased risk of early complications after implantation of a pacemaker but are at lower risk for lead fracture	Any early complication occurred in 5.1% of patients >=75 years of age compared to 3.4% of patients aged <75 years (P = 0.006)	2	1	1
Bonati 2011	3	3,433	69	Endarterectomy (CEA) was safer for symptomatic carotid stenosis in the short-term than stenting (CAS), because of an increased risk of stroke associated with stenting in patients over the age of 70 years. Stenting should be avoided in older patients	In patients <70 years old the 120-day stroke or death risk was 5.8% in CAS and 5.7% in CEA (RR 1.00, 0.68-1.47); in patients 70 years or older, there was an estimated two-fold increase in risk with CAS over CEA (12.0% vs. 5.9%, RR 2.04, 1.48-2.82)	2	1	1
Bristow 2000	NR *	65	65	The amount of residual disease after cytoreductive surgery, age, and performance status appear to be important determinants of survival in patients with Stage IVB endometrial carcinoma	Age above 58 years was associated with a poorer survival	2	1	1
Chen 2000	2	40,000	67	Early aspirin is of benefit for a wide range of patients, and its prompt use should be routinely considered for all patients with suspected acute ischemic stroke, mainly to reduce the risk of early recurrence	Older patients were not at particular risk of recurrent ischemic stroke or of hemorrhagic stroke, so the absolute net benefits of early aspirin appear to be about as great for them as for other types of patients	1	1	1
Cohen 2009	5	319	NR	Clinical parameters that appear to predict response to epidermal growth factor receptor inhibitors (EGFR) in recurrent and metastatic squamous cell carcinoma of the head and the neck include performance stage and age	Older age was associated with longer progression free survival and overall survival	4	2	1
De Boer 2010	22	6,763	NR[4]	In this analysis of randomized trials, the reduction in clinical end points by percutaneous coronary intervention (PPCI) was not influenced by age	The point estimate of treatment effect of PPCI vs. fibrinolysis (overall adjusted OR: 0.65; 95% CI: 0.52 to 0.79) was compatible with a mortality reduction favoring PPCI in all age strata	1	1	1
DIPART group 2010	7	68,517	70	Calcium and vitamin D given together reduce hip fractures and total fractures, and probably vertebral fractures, irrespective of age, sex, or previous fractures	No interaction was found between fracture history and treatment response, nor any interaction with age, sex, or hormone replacement therapy	1	3	1
Early Breast Cancer Group 2000	40	19,682	NR	Radiotherapy regimens (…) would be expected to produce an absolute increase in 20-year survival of about 2–4% for early breast cancer. The average hazard seen in these trials would, however, reduce this 20-year survival benefit in young women and reverse it in older women	At least for 20-year survival, the overall balance of benefit and risk with the main types of radiotherapy in these trials is likely to be unfavorable for older women	2	1	3
EBCTC Group 2010	4	3,729		After 10 years of follow-up, there was no significant effect (of adjuvant radiotherapy vs. no radiotherapy following local excision for DCIS) on breast cancer mortality, mortality from causes other than breast cancer, or all-cause mortality	Radiotherapy resulted in a larger proportional reduction in the rate of ipsilateral breast recurrence for women aged more than 50 years than for younger women	4	1	1
EBCTC Group 2011	20	21,456	NR	5 years of adjuvant tamoxifen safely reduces 15-year risks of breast cancer recurrence and death. Estrogen receptor status was the only recorded factor importantly predictive of the proportional reductions	The proportional risk reductions were slightly, but not significantly, greater at older ages, but benefits were substantial and consistent for women in each age range	4	2	1
ESDT 2005	11	1,597	66 to 78	Appropriately resourced Early Supported Discharge (ESD) services provided for a selected group of stroke patients can reduce long term dependency and admission to institutional care as well as reducing the length of hospital stay	There was no significant association of patient age or gender with the apparent effect of the ESD service	1	1	1
Entsuah 2001	8	2,045	42	Men and women have comparable responses to selective serotonin reuptake inhibitor (SSRIs) and venlafaxine across various age groups	None of the efficacy measures were influenced by patient age	1	1	1
Farmer 2012	6	2,552	60	Evidence was not convincing for a clinically meaningful effect of clinical management of non-insulin treated type 2 diabetes by self-monitoring of blood glucose levels compared with management without self-monitoring	The difference in levels was consistent across subgroups defined by personal and clinical characteristics	1	1	1

Reference	No. of trials (n)	Total sample size (n)	Mean age year)	Authors' conclusions	Difference with younger/ total group	Categories for conclusion[q]	Absolute or relative risk[r]	Reason for IPD[s]
Flather 2000	3	12,763	61	This systematic overview shows that ACE inhibitors lower rates of mortality, myocardial infarction (MI), and hospital admission for heart failure in patients with left-ventricular dysfunction or heart failure with or without a recent MI	With stratification for age (<55 years, 55–64 years, 65–74 years, >75 years) there was no heterogeneity in the benefits of treatment for the combined outcomes of death or myocardial infarction and death or readmission for heart failure	1	1	1
Fonseca 2010	6	2,095	54 to 58	Premix analog may be an appropriate choice to target HbA1c values in older individuals and those with higher bedtime plasma glucoses (PG)	Premix analog rather than basal insulin may be an appropriate choice to target HbA1c values in older individuals	3	3	1
Fox 2010	3	5,467	63	A routine invasive strategy reduces long-term rates of cardiovascular death or myocardial infarction and the largest absolute effect in seen in higher-risk patients	The largest absolute difference in cardiovascular (CV) death or MI, and in all-cause and CV mortality, was seen in the highest risk group, off which age was one of the indicators. Univariable associations with CV death or MI: per 5-yr increase HR 1.25 (1.20-1.29)	4	2	3
Früh 2008	5	4,584	NR	Adjuvant cisplatin-based chemotherapy should not be withheld from elderly patients with non-small-cell lung cancer purely on the basis of age	Elderly patients, who met the eligibility criteria for trial enrollment, had a survival benefit from chemotherapy that was similar to that of their younger counterparts	1	1	1
Healey 2007	3	1,866	64	In elderly patients with a history of life-threatening ventricular arrhythmias, the ICD may not afford the same survival advantage over amiodarone that is seen in younger patients.	In patients < 75 years old, the ICD significantly reduced both all-cause (HR = 0.69, 95% CI: 0.56–0.85) and arrhythmic death (HR = 0.44, 95% CI: 0.32–0.62). Neither benefit was clearly observed in the group of patients ≥ 75 years old (HR = 1.06, 95% CI: 0.69–1.64, and HR = 0.90, 95% CI: 0.42–1.95)	2	1	1
Hlatky 2009	10	7,812	NR	Long-term mortality is similar after CABG and PCI in most patient subgroups with multivessel coronary artery disease, so choice of treatment should depend on patient preferences for other outcomes	CABG might be a better option for patients with diabetes and patients aged 65 years or older because we found mortality to be lower in these subgroups	3	1	1
Jeger 2011	2	348	65 .7	Only two RCT about the effect of early revascularization (ERV) have been published emphasizing the difficulty of enrolling critically ill patients	ERV benefit is similar across all ages and not significantly different for the elderly. There was no significant difference in the treatment effect by age (≤75 years relative risk at one year 0.79, 95% CI: 0.63-0.99; > 75 years relative risk at one year 0.93, 95% CI: 0.56-1.53)	1	2	1
Margolis 2000	5	568	58	A standard care regimen for diabetic neuropathic foot ulcers is most likely to be effective for patients who have wounds that are small and of brief duration.	The patient's age (OR = 0.99; 95% CI, 0.89-1.01) was unassociated with the probability of wound healing.	1	2	1
MTCG Group 2001	24	4,012	NR	This overview shows that interferon (INF) delays disease progression and that, even after several years, there still appears to be a persistent reduction in the likelihood of having suffered recurrence	There was no evidence, from any of these variables, that the benefit of IFN was importantly greater or worse in either good- or poor-risk patients	1	2	3
Raftopoulos 2005	15	643	53	Age, gender, surgical technique, means of access, and rectopexy method had no impact on recurrence rates following abdominal surgery for full-thickness rectal prolapse	Idem	1	1	1
Rothwell 2011	8	25,570	NR	Daily aspirin reduced deaths due to several common cancers during and after the trials	Benefit increased with age-the absolute reduction in 20-year risk of cancer death reaching 7·08% (2·42-11·74) at age 65 years and older	4	1	2
Sargent 2001	7	3,351	NR	Selected elderly patients with colon cancer can receive the same benefit from fluorouracil-based adjuvant therapy as their younger counterparts, without a significant increase in toxic effects	The incidence of toxic effects was not increased among the elderly (age >70 years), except for leukopenia in one study	1	1	1
Simmonds 2000	13	1,365	NR	Chemotherapy is effective in prolonging time to disease progression and survival in patients with advanced colorectal cancer	No age related differences were found in the effectiveness of chemotherapy, but elderly patients were underrepresented in trials	1	1	1

q= 1= Older and younger people should receive the same treatment; 2= Treatment should be avoided in older patients/ older patients have a higher risk for complications; 3= Older people should receive another treatment than younger people; 4= Treatment is more effective in older patients. **r**= 1= absolute; 2= relative; 3= unclear.**s**= 1= Subgroup analysis for age; 2= Extra information needed; 3= time to event analysis; 4= other. *= NR= Not reported

Table 1b: Summary of the 8 IPD reviews that included only older patients

Reference	No. of trials (n)	Total sample size (n)	Mean age (year)	Authors' conclusions	Reason for IPD*
Fayers 2011	6	1,685	69 to 78	Thalidomide added to melphalan and prednisone improves overall survival and progression-free survival in previously untreated elderly patients with multiple myeloma, extending the median survival time by on average 20%	2
Gauthier 2010	6	2,183		Functional data were successfully pooled using standardizing methodology. A beneficial effect of donepezil treatment on function was demonstrated using this standardized functional scale	5
Jones 2009	13	3403	74	Patients are showing slower rates of cognitive decline in more recent trials of donepezil, compared with older trials, although having more comorbidities	2
Labarere 2006	2	1310	83	Prophylaxis with graduated compression stocking is not associated with a lower rate of deep vein thrombosis in nonsurgical elderly patients in routine practice	2
Mallen 2011	21	9,461	72	Among elderly arthritis patients, the incidence of gastrointestinal intolerability adverse events was lower with celecoxib than with naproxen, ibuprofen, or diclofenac	1
De Morton 2007	9	NR	NR	This study indicates that older persons who are admitted to acute care medical settings and who required supervision or assistance to ambulate at admission are the most responsive to additional exercise during hospitalization	3
Schneider 2005	2	202	72	A specific stress-decreasing approach used in the prevention and control of high blood pressure, such as the Transcendential Mediation program, may contribute to decreased mortality from all causes and cardiovascular disease in older subjects who have systemic hypertension	4
Whitehead 2004	10	2376	72	Donepezil (5 and 10 mg/day) provides meaningful benefits in alleviating deficits in cognitive and clinician-rated global function in AD patients relative to placebo	5

* 1= subgroup analysis for age; 2 = subgroup for other characteristics than age; 3= extra information needed; 4= time to event analysis; 5= other

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Acetaminophen for self-reported sleep problems in an elderly population (ASLEEP): a randomized double-blind placebo-controlled trial

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Abstract

Objectives: To investigate whether acetaminophen is effective in treating self-reported sleep problems in the elderly.

Design: Double-blind placebo-controlled randomized clinical trial (1:1)

Setting: Primary care

Participants: 61 individuals aged 65 years or older with self-reported sleep problems. Eligible participants should be able to give informed consent, should not be severely cognitively impaired (MMSE ≥ 20), should not have pain and should not use acetaminophen on a regular basis because of pain complaints.

Intervention: After a baseline week, acetaminophen 1000 mg or placebo at bedtime for a period of two weeks was randomly allocated by means of a computer-made randomization list. Participants, investigators and analysts were blinded to group assessment until the end of the study.

Measurements: The primary endpoint was the self-reported sleep at the end of the study, as measured by the Insomnia Severity Index (ISI).

Results: Between July 2011 and December 2012, 61 participants were enrolled and randomized. The median age was 73 years; 90% of the people lived at home and few had co-morbidities as reflected by the Charlson comorbidity index. There were no differences between the intervention (n=28) and control group (n=28) in the mean score on the ISI at the end of the study (14.3 vs. 15.3, p=0.38).

*Conclusion*s**:** In this small sample, treatment with acetaminophen did not improve the severity of sleep problems. Thee participants were heterogeneous; consequently, we might have missed an effect. Although there is no evidence available that justifies the prescription of acetaminophen to people with sleep problems, older people who use acetaminophen as an over-the-counter drug and feel they benefit from its use can better continue acetaminophen than start benzodiazepines.

Introduction

The prevalence of sleep problems is high in older people. In the Established Populations for Epidemiologic Studies of the Elderly (EPESE), involving 9,282 community-dwelling persons aged 65 and older, 50% reported sleep complaints, of which 25% had insomnia(1). In a study among 1503 older patients in primary care practices, the most commonly reported sleep-related complaints were difficulty sleeping (45%), snoring (33.3%) and excessive daytime sleepiness (27.1%)(2). People with insomnia report a negative impact on quality of life (3).

There are various hypotheses why older people suffer from sleep problems. Medical conditions such as depression, cardiovascular diseases, and pulmonary problems can interfere with a good night's rest. In addition, older people often use medication that causes sleep problems, such as beta blockers and psychopharmacological drugs(4). Furthermore, some older people suffer from changes in circadian rhythm, because of which they feel sleepy in the early evening and / or awake early (4).

The pharmacological approach of sleep problems is only advised if nonpharmacological measures had insufficient effect (4;5). Many older people are prescribed sedative benzodiazepine as a hypnotic, although they are at increased risk for harmful side effects because of the age-related pharmacodynamic and pharmokinetic changes (6). Adverse events, such as falls (7;8), cognitive impairment (9) and drug dependence (10) and even an risk of death are reported (11). Considering the major health impact, the complexity and the high prevalence in often vulnerable patients, sleep complaints are an important area of investigation and simple treatments with fewer side effects are urgently needed.

In geriatric clinical practice, we have noticed that older community dwelling patients use acetaminophen for chronic sleep problems without having specific underlying pain complaints. In a survey of 176 elderly people, 48% stated that they used non-prescription products for sleeping problems. Nineteen percent of the individuals who had used a non-prescription product used acetaminophen (12).

Although in the literature we did not find any trials or observational studies that report the effect of acetaminophen on sleep problems, there are some ideas as to why this medication might have a positive effect on sleep. Possibly, acetaminophen relieves unrecognized pain complaints during the night. Another hypothesis is that after metabolisation in the brain, the breakdown product of acetaminophen reinforces the activity of the cannabinoid receptors, which in turn reinforce the activity of the serotonergic system (13;14). Acetaminophen lowers body temperature, also related to better sleep (15). Finally, its purported effect could be mainly placebo.

We performed a randomized controlled trial named ASLEEP - Acetaminophen for SLEep Problems in Elderly Patients. The aim of this trial was to investigate whether acetaminophen has a beneficial effect on self-reported sleep problems in older people. In addition, in order to validate the subjective sleep parameters against objectively measured indices of the sleep-wake pattern, we aimed to study the effects of

acetaminophen on periods of wakefulness and sleep as measured by means of an actiwatch in a subgroup of our participants (16).

Methods and design

Trial design

This was a phase 3, investigator-initiated, multicenter, stratified (per center, with balanced randomization (1:1)) double-blind, placebo-controlled trial, conducted in the Netherlands, between July 2011 and December 2012 (three sites). Full details of the study protocol are described elsewhere(17). After trial commencement, an amendment was made to the protocol in order to enhance recruitment: both visitors to the outpatient clinic could be enrolled, as well as respondents to advertisements in local newspapers. The study was carried out in compliance with the Helsinki Declaration and Good Clinical Practice guidelines and approved by the Medical Ethics Committee of the Academic Medical Center. The executive boards of the other participating centers, the Slotervaart Hospital and Gelre Hospitals, provided local feasibility approval. Written informed consent was obtained from all participants. No data safety and monitoring board was installed, because acetaminophen was considered safe. This trial was registered at the Netherlands Trial Register (NTR2747).

Participants and setting

The study population comprised people aged 65 years and older who complained of disturbed sleep. Participants could be either patients that visited one of the participating hospitals' outpatient clinics, or subjects recruited after advertising in local newspapers. The visitors of the outpatient clinic were enrolled during their visit; the respondents to the advertisements were invited to come to one of the participating hospitals for the intake.

Sleep problems were defined as one or more of the following symptoms: difficulties with falling asleep, maintaining sleep and early awakenings without being able to fall asleep again, with a frequency of at least three nights a week, at least during three consecutive weeks (18). Eligible participants should have a score of five points or more on the Pittsburgh Sleep Quality Index (PSQI) (19). This is a validated instrument that assesses sleep quality and disturbances over a one-month time interval. A global PSQI score greater than five yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleepers (19). Further inclusion criteria were: a score of 20 points or more on the Minimal Mental State Examination (MMSE) (20) and participants had to be willing and medically able to receive therapy according to the protocol for the duration of the study. In addition, participants should be able to give informed consent themselves.

Exclusion criteria were the inability to speak, understand or write Dutch, the inability to follow the study procedures as assessed by the researcher, alcohol abuse (≥ four units daily), pain complaints resulting in a pain score of six or higher at the visual analogue (VAS) scale, impaired liver function as reflected by increased ALAT or liver disease in the past,

suicidal tendencies and participation in other sleep trials. Use of acetaminophen and not being able to stop this medication during the study period was a reason for exclusion as well. In addition, participants with a life expectancy less than three months according to the physician or with a sleep problem due to a medical or somatic reason (such as obstructive sleep apnea syndrome, restless legs, delirium, or a depression needing the start of antidepressants) were excluded.
The inclusion took place at the outpatient clinics of one of the participating hospitals: the Academic Medical Center in Amsterdam (a major teaching hospital), and of two regional teaching hospitals, the Slotervaart Hospital in Amsterdam and Gelre Hospitals in Apeldoorn. During the study period, participants were at home.

Interventions
The study period per participant was three weeks. Use of study medication was limited to the last two weeks to enable baseline data collection in the first week. In the second and third week they took either acetaminophen, or placebo, once per day at bedtime. The medication comprised two tablets containing either 500 mg of acetaminophen (Pharmacy the Hague hospitals, The Netherlands) or a matched placebo. In the sleep diary, participants registered whether they had taken the study medication the night before. Participants who already used acetaminophen as a sleeping pill were asked to stop the medication for the complete study period of three weeks.
Participants were allowed to continue their own chronic prescriptions, including their sleeping pills. Apart from the study medication, participants were asked not to start new sleeping pills or acetaminophen as a painkiller during the study period. Participants were excluded if they took sleeping pills of acetaminophen despite these restrictions. After exclusion, the study medication was stopped, but data collection was continued.

Data collection
At baseline, demographic data, medical history and present medication use were recorded. Functional status was assessed using the 15-item modified Katz Index of Activities of Daily Living (ADL) based on the situation two weeks prior to admission. Furthermore, sleep parameters registered in the sleep diary and the Insomnia Severity Index (ISI) after the first study week were registered. The severity and number of comorbidities was scored using the Charlson comorbidity index (21).

Outcomes
The primary outcome was the mean score on the Insomnia Severity Index (ISI) at 21 days (22;23). The ISI is a reliable and validated instrument for the evaluation of self-reported sleep-problems, and has also been investigated among seniors. It is a 0-28 point scale, the higher the score, the more sleep complaints a patient has (24-26). The following categories are used to classify sleep complaints: 0-7: not clinically significant, 8-14: sub treshold insomnia, 15-21: moderate insomnia and 22-28: severe insomnia. A minimal

important difference of 6 points on these scale has been reported (25);we assumed a decrease or increase of three points compared to baseline on this scale as clinically relevant because we were interested in a small effect as well.
We intended to measure objective sleep parameters as secondary outcome, registered by means of an actiwatch (16;27). Detailed description of the actiwatch method can be found in the protocol (17).
In addition to this, all participants recorded in a sleep diary the time they got into and out of bed, the estimated time they fell asleep and woke up in the morning and the number of awakenings during the night. These data were used to estimate the following sleep/wake endpoints: total sleep time (minutes sleep between bedtime and wake time), sleep efficiency (percentage of time asleep while in bed), sleep onset latency (minutes awake between sleep onset and wake time) and number of wake episodes (16). Furthermore, participants daily registered a pain score by means of a 10 cm visual analogue scale (VAS) and rated their sleep quality with a score of 0-10. The registrations of the first week (mean values), when participants used no medication, were compared with the mean values of the second and third week taken together.

Sample size
The primary endpoint were subjective sleep problems, as reflected in the score on the ISI at the end of the third week of the two groups. From the literature, a prevalence of sleep problems of 30%-50% is reported (1) . Group sample sizes of 75 per group were assumed to achieve 80% power to detect a difference of three points on the Insomnia Severity Index between the null hypothesis that both group mean differences are zero and the alternative hypothesis that the mean difference of the intervention group is three with assumed group standard deviations of 6.5. This calculation was based on data from a study in which a group of participants with insomnia were treated with either eszopiclone or placebo (28).

Randomization and masking
After baseline assessments, participants were randomized to acetaminophen or a matched placebo treatment that looked, tasted and smelled the same. Randomization was stratified by study center, with fixed blocks of 10 participants within the stratum. Before the start of the study, the randomization schedule was generated with a computer by an independent statistician; the randomization list was maintained by the trial-pharmacist. The medication was provided in sequentially numbered containers according to the randomization list. Study medication was manufactured and packaged in small containers labeled according to Good Manufacturing Procedure (GMP) guidelines. Investigators, other staff personnel and participants remained blinded until the last participant had completed the study and the data analysis had been completed.

Statistical methods

Data were analyzed according to the intention-to-treat principle. The outcome measures were tested by using T-Tests and Mann-Whitney Tests for continuous variables and by using Chi-squared tests for categorical outcomes. We performed a pre-specified subgroup analysis for participants using sleeping pills at baseline and those who did not and for study center. The primary outcome, the score on the Insomnia Severity Index, was used as a continuous variable. Furthermore, we performed multivariate logistic regression for factors that might have an influence on the sleep quality, such as coffee and alcohol use and pain; as well as for baseline imbalance.

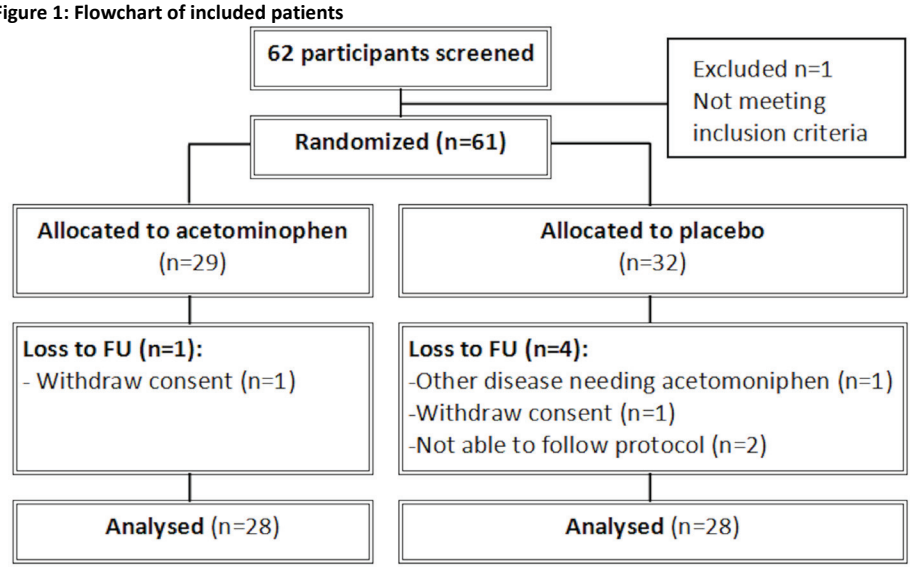
Analyses were performed with the program Statistical Package for the Social Sciences (SPSS) version 20.0. P values <0.05 were considered statistically significant.

Results

Participants, recruitment and baseline data

Between July 2011 and December 2012 61 participants were eligible and gave their consent. After randomization, five participants were excluded or ended the study prematurely (Figure 1).

Figure 1: Flowchart of included patients



Unfortunately, no data were available for the participants who were lost to follow-up. Therefore, 56 participants were analyzed: 28 participants in the placebo-group and 28 in the acetaminophen group. Baseline characteristics were well matched among the two study groups (Table 1).

Table 1: Baseline characteristics of enrolled patients

	Acetaminophen (n=29)	Placebo (n=32)
Age ((year), median, range)	73.0 (65-89)	74.0 (65-88)
Sex (% male)	48.3	34.4
Country of birth the Netherlands (%)	82.8	93.8
Living single (%)	51.7	43.8
Living independently (%)	89.7	90.0
Katz score (median, (range))	0 (0-9)	0 (0-3)
Charlson comorbidity index (median, (range))	1 (1-3)	1 (1-3)
No. of medications (median, (range))	5 (0-15)	3 (0-17)
Beta blockers n (%)	11 (37.9)	5 (16.1)
Sleeping pills[1] n (%)	6 (20.7)	9 (28.1)
Pain killers n (%)	6 (20.7)	9 (28.1)
MMSE[2] (median, range)	29.0 (21-30)	30 (26-30)
MMSE ≤ 24	1	0
BMI[3] (mean (SD[4]))	27.8 (6.7)	25.6 (5.0)
Alcohol consumption yes n (%)	21 (72.4)	18 (56.3)
No. of alcoholic consumptions per day (SD)	1.5 (0.9)	1.5 (0.9)
Coffee consumption n (%)	24 (82.8)	28 (93.3)
No. of coffee consumptions per day (SD)	3.6 (2.0)	3.5 (1.8)
PSQI[5] (mean (SD))	13.0 (3.1)	13.0 (3.2)
Mean VAS[6] for pain during 1st week (median, range)	0.26 (0-5.2)	0.85 (0-5.9)
ISI[7] at 7 days (mean (SD))	14.9 (4.6)	15.5 (3.7)
Mean total sleep time first week, hours (mean/SD))	6.0 (1.5)	5.6 (1.3)
No. of awakenings 1st week (mean (SD))	2.1 (1.0)	2.6 (1.2)
Sleep onset latency 1st week (minutes, median, (range))	49.3 (2.9-309.2)	58.9 (13.1-220.0)
Sleep efficiency (%, (SD))	70.4 (16.7)	68.5 (16.5)
Mean mark for night's rest 1st week (median, (range))	5.8 (1.0-7.3)	5.6 (3.1-6.9)

[1]Melatonin, benzodiazepines, zolpidem, zopiclon / [2]Minimal mental state examination / [3]Body Mass Index / [4]Standard Deviation / [5]Pitssburgh Sleep Quality Index / [6]Visual Analogue Scale; the reported value is the mean of the seven VAS that patients scored daily / [7]Insomnia Severity Index

Table 2: Outcomes

	Acetaminophen (n=28)	Placebo (n=28)	P-value
Primary outcome			
ISI[8] at 21 days (mean (SD[9]))	14.3 (4.3)	15.3 (3.7)	0.38
Mean difference ISI week 2/3 minus. week 1 (SD)	-0.24 (3.5)	0.00 (2.7)	0.78
Secondary outcomes			
Mean total sleep time last two weeks, hours (mean (SD))	6.1 (1.3)	6.0 (1.2)	0.70
No. of awakenings 2nd and 3rd week (mean (SD))	1.9 (1.0)	2.4 (1.1)	0.09
Sleep onset latency 2nd and 3rd week (minutes, median)	50.4 (10.7-323.6)	61.3 (5.8-161.8)	0.68
Sleep efficiency (%, (SD))	71.9 (15.2)	70.6 (13.4)	0.67
Mean mark for night's rest (median, (range))	5.64 (3.1-7.0)	5.8 (1.0-7.9)	0.98
Mean VAS[10] for pain 2nd and 3rd week (median, range)	0.21 (0-5.37)	0.34 (0-6.44)	0.52

[8]Insomnia Severity Index / [9]Standard Deviation / [10]Visual Analogue Scale

Median age was 73 years, 90% lived at home before admission and only one participant had an MMSE ≤ 24. Most participants were in good health, considering their low score on the Katz ADL index and the Charlson comorbidity-index.

Outcomes

No significant effect of acetaminophen on sleep problems could be demonstrated for the primary outcome: ISI at 21 days (Table 2).

Pre-specified subgroup analysis for participants who used sleeping pills at baseline (n=15) did not show differences (mean difference on Insomnia Severity Index 1.8 (95% confidence interval (CI) (1.6-5.0); neither did subgroup analysis for participants using pain killers ((n=15): the mean difference between the ISI at baseline and after the end of the study was 0.6 (95% CI 2.5-5.0).

Furthermore, in an exploratory analysis we investigated whether there was a difference between both groups in the number of participants whose score on the ISI increased or decreased. Again, there was no difference; in both the acetaminophen and placebo groups the distribution of participants whose score increased and whose score decreased was the same: in the placebogroup 9 participants had a lower score on the ISI after three weeks, and in the intervention group 11 participants

Logistic regression, adjusted for the stratification variable (treatment center) did not show a decrease on the ISI) (Odds Ratio (OR) = 0.64, 95% CI 0.22-1.90). Furthermore, multivariate logistic regression (adjusted for factors that might influence sleep such as use of coffee and alcohol and for VAS, as there was a slight difference at baseline between the two groups) neither showed a treatment effect (OR = 0.92 (95% CI 0.29-2.93).

The secondary outcomes, the sleep parameters described in the sleep diary, were not statistically significant between groups (table 2). Unfortunately, the participants that were lost to follow-up (n=5) did not complete the protocol, usually for logistic reasons. Therefore, an intention-to-treat analysis was not possible. No harms were reported during the study period.

Unfortunately, the intended subgroup that used the actiwatch consisted of only five participants. This was mainly caused by logistic failure. In this small group, a non-significant increase of total sleep time (31 minutes) and a decrease of sleep onset latency (17 minutes) were shown in the treatment group (n=3).

Discussion

In this randomized double-blind placebo controlled clinical trial involving older participants with subjective sleep problems we found no effect of acetaminophen on the incidence and severity of sleep disorder. However, our sample was small and heterogeneous, therefore we might have missed an effect. Although there is no evidence available that justifies the prescription of acetaminophen to people with sleep problems, older people who use acetaminophen as an over-the-counter drug and feel they benefit from its use can safely continue acetaminophen. The effect for this group is probably mainly placebo.

It is known that performing research in older patients is difficult (29). The patients that visited the outpatient clinic of the participating hospitals often were not eligible because of cognitive impairment. Although many confirmed they had sleeping problems, they

usually gave priority to their other health problems and therefore considered the burden of participation in a trial as too big. Possibly, many potentially eligible patients considered their sleep problems as something that naturally occurs at older age and therefore did not want to participate. To enroll more participants, we had to expand our study population to people that responded to advertisements put in local newspapers. As a consequence, the participants in our study were generally younger and had fewer co-morbidities than the general population of geriatric outpatient clinics. Even though we designed the trial in such a way that the expected burden was as low as possible, we did not succeed in enrolling enough geriatric patients.

Maybe enrolling patients visiting an outpatient clinic is not the most appropriate method, since they often are referred for more urgent other complaints. Possibly, performing this kind of trial in general practice and following up these patients by home visits would have resulted in a higher number of participants.

Our study was underpowered to demonstrate a treatment effect. Therefore it is difficult to define the exact role of acetaminophen in the management of sleep problems. Appropriate treatment of sleep problems should start with nonpharmacologic interventions; pharmacologic treatment should only be started if indicated (30). Data suggest a slightly positive effect of cognitive behavioral interventions for insomnia in older people (31). Some authors recon that bright light therapy might help, because many poor sleepers have a disrupted cycle of their circadian rhythms; however there are no randomized trials available to base this conclusion on (32). Also, no trials were designed to test the effectiveness of physical exercise for the treatment of sleep problems in healthy older people (33). For patients with dementia, there is evidence that melatonin might be effective in circadian rhythm disturbances, thereby reducing sundowning (34). More studies are needed to establish the appropriate role and use of medications, and their safety and efficacy in the treatment of insomnia in older adults. Guidelines that direct the choice and use of pharmacologic and nonpharmacologic therapies are needed (35).

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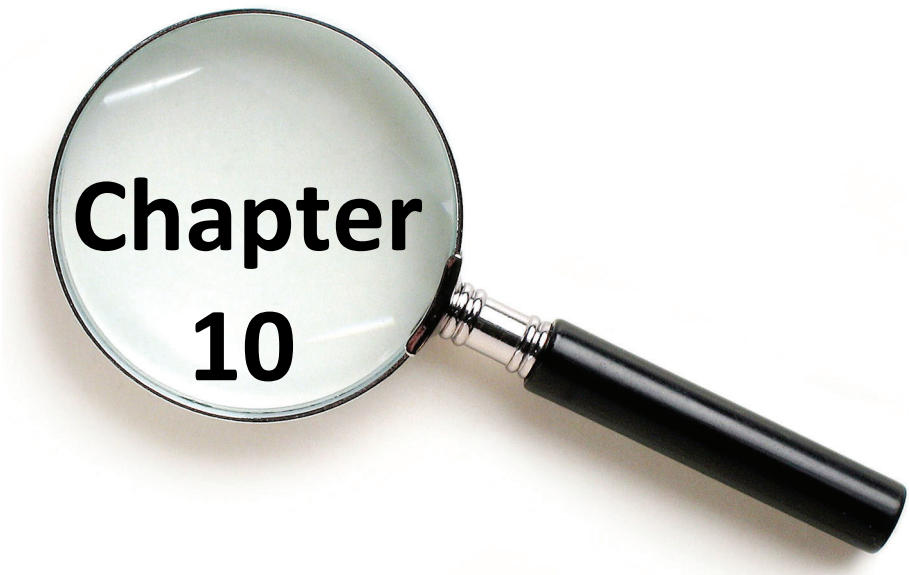

Older people's barriers and facilitators to participation in a placebo-controlled randomized clinical trial

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Abstract

Objectives: To explore the barriers and facilitators of older people and their primary caregivers to participate in the MAPLE study, a placebo-controlled randomized clinical trial (RCT) on the efficacy of melatonin for the prevention of delirium in elderly hip fracture patients.

Design: Descriptive survey.

Participants: All consecutive patients eligible for participation in the MAPLE study.

Measurements: Participants were semi-structurally interviewed at admission to record their motivations or barriers to participate in the trial regardless of their informed consent. If the patient was not able or not willing to answer the questions, the primary caregiver was asked to participate.

Results: We evaluated the data of 195 participants and 92 non-participants, and caregivers were interviewed in 52% and 75% of the cases, respectively. The participants were more often institutionalized, used more medication and had more co-morbidities. The most important facilitators to participate were a positive attitude toward research in general, the belief that this study was useful, and altruism. The most important barriers were the performance of the blood test, the use of extra medication and the expected burden in general. Surprisingly, the majority of the participants considered the blood test useful.

Conclusion: Trials that are considered to be more useful and do not lead to extra burden are expected to have a better inclusion rate.

Furthermore, because the blood test was one of the major barriers to participation, the reason for taking extra blood may require more clarification to clarify wrong ideas and misperceptions.

Introduction

With an aging population and increased life expectancy, the care and treatment of older people are a high burden on health care provision. Especially in more developed regions, the number of older people is growing at a faster rate than ever before. Almost 33% of the population in these regions is projected to be 60 years or over, up from 22% in 2009(1). Because aging of the population is often accompanied by the development of multiple chronic illnesses, this places a high financial burden on society.

Older people are underrepresented in practically all medical research (2;3). This lack of scientific evidence creates major difficulties in translating research into daily clinical geriatric practice, often resulting in prescribing drugs to vulnerable patient groups without knowing exactly whether the dose or frequency should be adjusted. In addition, older people are more vulnerable to adverse drug events due to alterations in pharmacodynamics and pharmacokinetics.

The reasons for excluding older people from clinical trials and other research vary. Often, age limits are set without justification (3) because researchers fear that older people are less capable of adhering to research protocols, thereby increasing the number of drop-outs in their study (4;5). In addition, researchers may have concerns about older people recalling information (6) or their ability to provide a legal informed consent (7). In addition to age limitations, eligibility criteria, such as (other) co-morbidities, drug use or decision incapacity, often automatically exclude older people (8). Even after overcoming these barriers, it remains challenging to find appropriate numbers of participants to generate and test a representative sample of the target population (4).

Therefore, it would be interesting to determine older people's incentives toward participating in clinical trials, especially in a challenging design, such as in placebo-controlled and randomized clinical trials. Moreover, not only are the patient's considerations important, primary caregivers can also play an important role in engaging or disengaging older people in research (9;10).

From the literature, it is known that although 'altruism' is a strong motivator of older people, they are often held back from participation by problems such as cognitive impairment, ethnic differences between researchers and potential research subjects, health problems and being unwilling to take extra or unknown (placebo) medication (9-11). Awareness of these and other attitudes is a crucial step toward designing effective recruitment strategies for designing studies involving older people.

In this study, we aimed to explore older people's perceptions of the facilitators and barriers toward participation in the MAPLE study (Melatonin Against PLacebo in Elderly patients), a clinical trial that investigated the efficacy of melatonin against placebo in the prevention of delirium (12). In addition, we investigated whether participants differed from eligible patients who did not give their consent for participation (non-participants) with regard to their age, sex, co-morbidities and other determinants. Finally, we explored the opinions of both participants' and non-participants' primary caregivers toward participation in a placebo-controlled and randomized clinical trial.

Methods

Study design

This study was a descriptive survey in which we explored the facilitators and barriers of patients and their primary caregivers toward participation in our study 'Melatonin Against PLacebo in Elderly patients' (MAPLE). The design of this study has been described in a previous publication (12). In brief, MAPLE was a randomized, placebo-controlled, double-blind, multicenter trial that investigated potential prophylactic effects of melatonin versus placebo on delirium in elderly hip fracture patients. Eligible patients were aged 65 years or older and should have been enrolled within 24 hours of admission and before surgery.

The population of this particular study consisted of all consecutive patients eligible for participation in MAPLE from January 2011 to April 2012. Patients who fulfilled the inclusion criteria were semi-structurally interviewed at admission to register their motivations or barriers toward participating or not participating in the trial, regardless of their informed consent. If the patient was not able or not willing to answer the questions, the primary caregiver was asked to participate. In some cases, both the participant and the caregiver were interviewed. Patients were separately asked for their consent for blood sampling.

Study procedures

We recorded demographic data, medical history, and the medication use of eligible patients who gave their consent for participation in the MAPLE study. Age, sex, living arrangements, home medications and co-morbidities were registered for both the participants and non-participants of MAPLE. The Minimal Mental State Examination (MMSE) (13) and Katz Activities of Daily Living (ADL) index (14) were also registered for the participants. Blood was taken to determine biomarkers. All data were registered anonymously.

To explore the motivators and facilitators that specifically applied to the MAPLE study, we developed specific questionnaires for both the participants and the non-participants with the help of an epidemiologist, a geriatrician and a research nurse. These questionnaires were based on behavioral change theories, with the basic assumption that behavior and decision making originate from a person's knowledge, attitude and past experiences (15-17). The structured questionnaire included the following items on participation in research: attitude toward scientific research in general, expectations of the usefulness of the study in general, expectations of personal benefit, and altruistic intentions. Furthermore, attitude and experiences with blood sampling were evaluated to determine whether the blood test affected the decision to participate because in this trial, the patients consented separately to blood testing (appendix 1, supplementary material). The response categories were 'agree', 'partially agree' or 'disagree'. As the non-participants did not consent for participation in MAPLE and therefore were not likely to be willing to respond to a long questionnaire, we modified and shortened the questionnaire.

Furthermore, some topics specifically applied to either the participants or the non-participants. Therefore, both lists differed, although some of the items could be compared.
An experienced research nurse conducted all recruitment and interview procedures. Once a patient was eligible for participation in MAPLE, the patients were interviewed for this survey as well. Likewise, the research nurse asked eligible patients who did not give their consent for their main reasons not to participate. If this person allowed further questions, the research nurse performed the interview to determine whether certain study components, such as medication, blood sampling, time consumption, expected burden, principled objections or previous experience with scientific research on melatonin, played a role in the decision not to participate (appendix 1, supplementary material). If a topic was not discussed in the interview, it was registered as 'not asked' and stated as a missing value.
If patients were unable to complete the questionnaires by themselves, their primary caregiver was asked for consent and invited to respond to the questionnaire.

Statistical analysis

For both the participants and non-participants, descriptive statistics were calculated for the barriers and facilitators toward participation. The mean age of participants and non-participants was compared using an independent T-test. The distribution of sex, living arrangements and co-morbidities between these groups was compared using the chi-square test. Logistic regression was performed to determine whether older age, co-morbidity or sex were univariably associated with the chance of participation. In addition, we investigated if the fact that patients were unable to complete the interview by themselves was associated with the chance of participation. We compared the questionnaires that were performed by the participants and their caregivers with a chi-square test. The categories 'agree' and 'partially agree' were combined. All analyses were performed with the program Statistical Package for the Social Sciences (SPSS), version 19.0.

Results

Sample characteristics

In the study period, 459 patients were screened for participation in the MAPLE study, of which 395 met the inclusion criteria. In total, 223 patients (56.3%) finally agreed to participate in this trial. During the entire MAPLE study period, approximately 60% of eligible patients gave their consent. In total, 195 participants and 92 non-participants completed the questionnaires (Figure 1).
The non-participants and participants were similar with regard to their age and sex (Table 1).

Figure 1: Flowchart of eligible patients

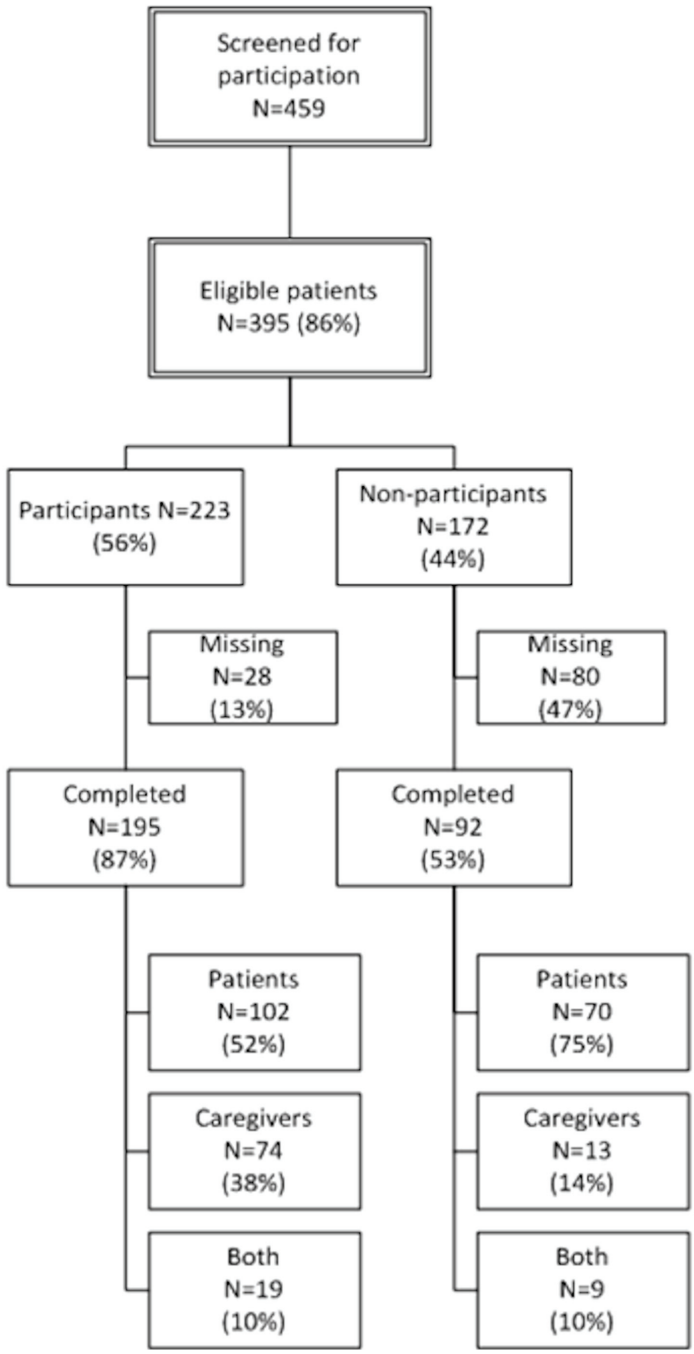


Table 1: Baseline characteristics

		Participants (n=195)	Non-participants (n=92)	
Mean age		84.2 (7.4)	84.2 (8.1)	p=0.99
Male (%)		22.6	26.1	p=0.55
Katz (%)	0-5 6-10 >10	40.8 15.7 2.4	Not reported	
Mean MMSE score (SD)		22.86 (6.8)	Not reported	
No of medications (mean (SD))		6.55 (2.5)	4.40 (3.2)	p<0.001
Missing, n (%)		29 (14.9)		
No of medications > 3 at admission, n (%)		116 (59.5)	42 (45.6)	p<0.001
Missing, n (%)		77 (39.4)	19 (20.7)	
No of medications >5 at admission, n (%)		64 (32.8)	26 (28.3)	P=0.12
Missing, n (%)		77 (39.4)	19 (20.7)	
Charlson score (% of participants)	0 1-2 3-4 ≥5	24.1 54.4 17.9 3.6	47.1 31.0 16.1 5.7	p<0.001
Living independently (%)		59	71	p<0.001
Questionnaire completed by	Patient (%)	52.3	76.1	p<0.001
	Caregiver (%)	37.9	14.1	
	Both (%)	9.7	9.8	

Participants were more often institutionalized, used more medication and had a higher Charlson co-morbidity index score (Table 1). Participants were significantly less able to complete the questionnaire by themselves than non-participants (52.3% vs. 76.1%, p<0.001).

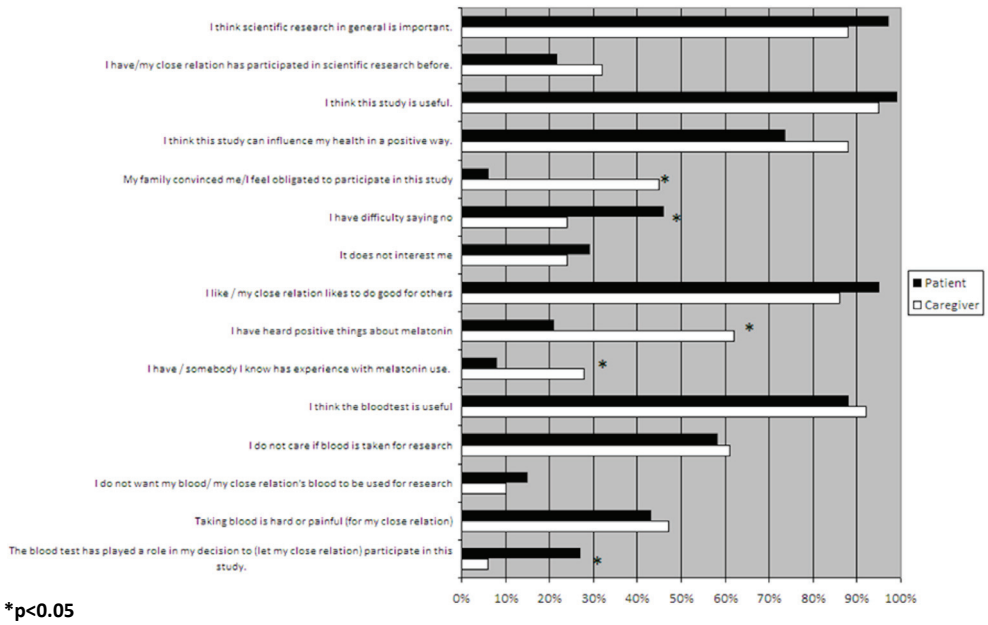
Logistic regression showed that age, sex, co-morbidity, and living arrangements did not influence the likelihood of participation in both univariate and multivariate analysis.

General questions - participants

We compared the questionnaires that were completed by the participants with the ones completed by the caregivers (Figure 2).

Questionnaires without missing data were available for 99 of the 102 patients (97%) and 69 of the 70 caregivers (93%) (Figure 1). An analysis of the questionnaires that were completed by both the patient and his or her caregiver was not possible due to too few data (n=19 and n=9, Figure 1). The motivators toward participation were similar for both patients and caregivers in most cases. Likewise, the majority of participants stated that they liked to do good for others. Almost all patients and caregivers considered scientific research in general as important and this particular study as useful. Many believed that the study could influence their health in a positive way. Patients experienced more difficulties saying no than the caregivers (p<0.001). Caregivers had more often heard positive information concerning melatonin (p<0.001) and had more experience with melatonin use (p<0.001). There were no differences between patients aged over 80 years and younger patients, except that the oldest old patients (> 80 yr.) had less frequently heard positive information regarding melatonin than younger patients.

Figure 2: Percentage agreement on questions for participants (n=99) and primary caregivers of participants (n=69)



***p<0.05**

Obtaining blood from participants

In addition to the general questions, the participants and primary caregivers were asked their opinion about the blood test (Figure 2). Data were available for 96 of 102 (94%) participants and 65 of 74 (88%) caregivers (Figure 1). The majority of participants and their caregivers agreed on the usefulness of the blood test. Although over 40% of the participants stated that they considered providing blood to be hard or painful, only a small number (7.2%) did not allow an extra blood test. Half of the patients in whom no blood test was performed refused permission for the blood test; in the other half, there were practical problems. Significantly more caregivers stated that the blood test played a role in their decision to let their close relation participate in the study compared to the participants themselves.

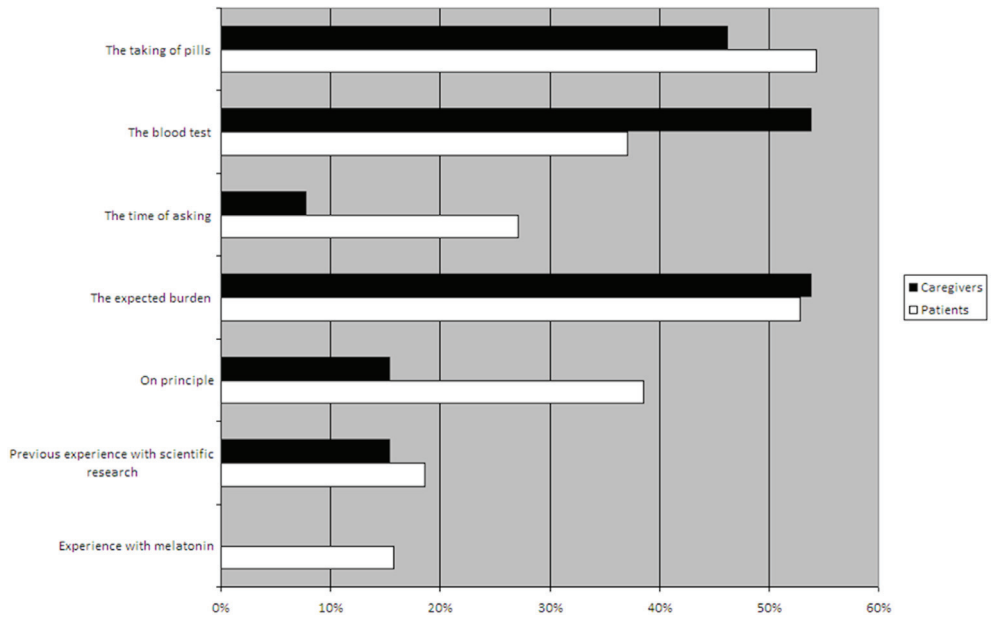
Barriers against participation

Patients and primary caregivers were asked about potential factors that may have contributed to their decision not to (let their close relation) participate in this clinical trial (Figure 3).

No significant differences were found between non-participants' and their caregivers' motivations or objections. The three highest ranking reasons for not participating for patients and their primary caregivers were the use of extra medication, the expected high burden and the extra blood test. For the oldest old patients (> 80 years), previous

experience with scientific research less frequently played a role in the decision not to participate. The extra blood test was the reason not to participate for 33% and 69% of non-participants and their caregivers, respectively (p=0.207).

Figure 3: Percentage agreement between participants (n=96) and primary caregivers (n=65) on questions for participants and primary caregivers



Discussion

In this study, we explored a number of potential facilitators and barriers of older people and their primary caregivers toward participation in a placebo-controlled randomized clinical trial. The most important facilitators for participation were a positive attitude toward research in general, the usefulness of this study in particular and altruism. The most important barriers against participation were the fact that a blood test was performed, the use of extra medication and the expected burden. The participants and the primary caregivers were similar with respect to their motivations, although the patients more frequently stated that they had difficulties saying no, and the caregivers more often felt obliged to let their close relation participate in the MAPLE study. There were no differences between the non-participants and the caregivers of non-participants regarding the reasons for not participating.

Considering the barriers, it was remarkable that the blood test was one of the major barriers against participation, even though most of the participants considered the blood test useful. A possible explanation might be that they believed this blood test would

function as an extra medical check-up. This theory is underlined by the finding that many of the participants believed that the MAPLE study could influence their health in a positive way. When performing research on older people, it might be a good idea to offer the blood test as an extra option, as we did in this particular study. However, the reason for taking extra blood may need more clarification to clarify wrong ideas and misperceptions.

Our findings are in accordance with the existing literature on facilitators and barriers of patients to participate in RCTs. In a recently published review on pharmacotherapy research in older adults, a positive attitude toward research and altruism were mentioned as the most important factors associated with more participation (9;18). Additionally, family member approval was listed as one of the most important facilitating factors. This highlights the importance of early and active involvement of the primary caregivers in the recruitment process. In addition, the following barriers are frequently described in the literature: a lack of knowledge about scientific research, fear of study-related injuries or falls, negative beliefs about medications and study interventions and study-related changes in routine (8;18;19). The current study agrees with these findings. The fact that primary caregivers' opinions were also taken into account in this study is noteworthy because research in this area is scarce. It was remarkable that the caregivers significantly more often felt obliged to let their close relation participate in the MAPLE trial. This could be explained by the fact that giving consent by proxy is more difficult than giving consent for yourself (20).

Furthermore, it was striking that the participants were more often institutionalized, used more medication and had more co-morbidities than the non-participants. A possible explanation might be that these patients expected more benefit from participation in the MAPLE study. The incidence of delirium is high among older hospitalized patients and many patients and primary caregivers may have experience with this unpleasant syndrome in either their social environment or earlier in life. Research in this area might more likely be labeled as useful by patients with poorer health.

Few prior studies have investigated the motivators of older people who did not give their consent for participation. To explore the motivators and facilitators that specifically applied to the MAPLE study, we developed the questionnaires ourselves. The main advantage of such a newly composed questionnaire is that it was specifically adapted to the MAPLE study. However, this implies that the results cannot easily be compared with other studies. In addition, as we developed questionnaires specifically applicable to the participants and the non-participants; therefore, not all the answers of the participants and non-participants were comparable. Because participants had to complete many questionnaires for the MAPLE study and were not always willing to complete another one, some of the data were missing. Regarding the non-participants, many of them did not give their consent for participation in the MAPLE study because of the expected burden. Consequently, many of them were not willing to complete the questionnaires for this study either. In light of this, it is positive that so much data were available for this group.

Conclusion

The MAPLE study presented an ideal opportunity for the exploration of facilitators and barriers of older people and their primary caregivers toward research. Many patients with delirium are functionally and cognitively impaired, making participation in a placebo-controlled randomized clinical trial even more difficult. With this exploration of attitudes of older people and their primary caregivers toward participation in a placebo-controlled randomized clinical trial, we believe that we have come one step closer to designing more effective recruitment strategies for older participants in medical research.

In accordance with previous studies, we concluded that the main reasons for older people and their caregivers to give their consent for participation were altruism, the usefulness of the study and scientific research in general. A novel finding was that the blood test was a barrier to participation, whereas it was considered relevant by patients who gave their consent.

Because the expected burden and the designed interventions of the trial were specific reasons for (not) participating, we advise paying extra attention and explaining these items before recruitment.

Appendix: Questionnaires

Items questionnaire participants (patient)

1. I think scientific research in general is important.
2. I have participated in scientific research before.
3. I think this study is useful.
4. I think this study can influence my health in a positive way.
5. My family convinced me/ I feel obligated to participate in this study.
6. I have difficulty saying no.
7. It does not interest me.
8. I like to do good for others.
9. I have heard positive things about melatonin.
10. I, or somebody I know, have/has experience with melatonin use.
11. I think the blood test is useful.
12. I do not care if blood is taken for research.
13. I do not want my blood to be used for research.
14. Taking blood is hard or painful for me.
15. The fact that blood is taken, has played a role in my decision to participate in this study.

Items questionnaire participants (primary caregiver)

1. I think scientific research in general is important.
2. My close relation has participated in scientific research before.
3. I think this study is useful.
4. I think this study can influence the health of my close relation in a positive way.
5. I feel obligated to let my close relation participate in this study.
6. I have difficulty saying no.
7. It does not interest me.
8. My close relation likes to do good for others.
9. I have heard positive things about melatonin.
10. I, or somebody I know, have/has experience with melatonin use.
11. I think the blood test is useful.
12. I do not care if blood is taken for research.
13. I do not want the blood of my close relation to be used for research.
14. Taking blood is hard or painful for my close relation.
15. The fact that blood is taken, has played a role in my decision to let my close relation participate in this study.

Items questionnaire non-participants

1. The taking of pills has played a role in the decision not to participate.
2. The blood test has played a role in the decision not to participate.
3. The time of asking has played a role in the decision not to participate.
4. The expected burden has played a role in the decision not to participate.

5. I do/my closest relation does not participate in scientific research on principle.
6. Previous experience with scientific research has played a role in the decision not to participate.
7. Experience with melatonin has played a role in the decision not to participate.

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General discussion and perspectives for future research

Introduction

The provision of optimal care to older people is a great challenge, because with increasing age the number of chronic diseases increases as well; the same holds true for the prevalence of cognitive and functional impairment (1;2). Scientific evidence applicable to this group of geriatric patients is scarce because elderly people tend to be underrepresented in all kinds of clinical research. The general aim of this thesis was to find ways to make the scarcely available evidence more accessible to clinicians and to develop opportunities to improve the use of evidence-based medicine (EBM) for geriatric medicine.

Identifying relevant evidence

The start of the EBM process is to turn clinical problems into well formulated clinical questions and then systematically search for contemporaneous research findings in the scientific medical literature (3). However, clinicians feel insecure about searching skills and they have limited time (4;5). In order to simplify searching databases, we developed search filters to identify evidence that is quickly and easily applicable to geriatric medicine (chapter 2). Our most sensitive search filter had a sensitivity of 94.8%, a specificity of 88.7%, and a precision of 73.0%; our most specific search filter had a specificity of 96.6%, a sensitivity of 69.1% and a precision of 86.6%. We have demonstrated that the majority of relevant articles were found by the sensitive search filter by checking the retrieval of references identified for lectures of a postdoctoral course (chapter 3). Using search filters with high quality can save time, because they increase the number of relevant records retrieved compared to the total number of records retrieved (precision), and they can improve the relevant yield (or sensitivity) of a search on the other hand (6).The yield of our search filters and the identification of scientific evidence that is relevant to the older population in general could be further improved by developing and assigning unambiguous Medical Subject Headings (MeSH terms) for publications concerning geriatric topics by indexers of literature databases such as MEDLINE.

In spite of the advantages of search filters, there is a low level of usage in clinical practice (4;7;8). A first (generic) step in promoting the use of search filters is to increase the awareness to the existence of such filters. This is for instance done by the InterTASC Information Specialists' Sub-Group Search Filter Resource; a collaborative venture to identify, assess and test search filters designed to retrieve research by study design or focus (9). By publishing search filters on their website, the use thereof among librarians and clinicians is promoted. Furthermore, by presenting our search filters on conferences and in the journal and on the website of the Dutch scientific geriatric association we aimed to increase the awareness. A second important step to increase the use of search filters is to teach searching skills in both the clinical and preclinical phase of medical training (10); using search filters should be part of this. In addition, using validated search filters of good quality should be part of reporting guidelines of systematic reviews, such as the PRISMA statement (11).

Even though for many relevant geriatric topics sound evidence is lacking, using our geriatric search filters could improve EBM in geriatric practice because the scarcely available literature will be identified more quickly and easily.

Availability of evidence applicable to geriatric medicine

Evidence-based clinical practice implies adhering to CPGs. However, geriatric patients pose challenges to the development and application of CPGs, because they usually suffer from more than one disease whereas CPGs usually focus on one single disease. In addition, different conditions coexisting within the same patient may interact, changing the risks associated with each condition and its treatments (1). Creating guidelines relevant to older people with multimorbidity is important because multimorbidity is associated with poor quality of life, physical disability, high health care use, multiple medications, and increased risk for adverse drug events and mortality (1;12).

In 2012, VERENSO, the Dutch Association of Elderly Care Physicians and Social Geriatricians, prepared an evidence-based multidisciplinary guideline concerning decision-making about cardiopulmonary resuscitation in frail elderly (13). On the instigation of VERENSO, we performed a systematic review to investigate the association between pre-arrest factors such as age, cognitive function and multimorbidity and the probability of survival and the quality of life of elderly (≥70 years) survivors after out-of-hospital cardiac arrest (OHCA). During this review process, we encountered many challenges. Firstly, the included studies were generally of low quality, especially with regard to the measurement of the outcomes and the account for possible confounding factors, preferably arrest factors such as witnessed arrest, emergency services' response time and whether the rhythm was shockable or not. Furthermore, due to considerable statistical and clinical heterogeneity, performing a meta-analysis of survival was only possible for a selection of the studies. In addition, information concerning functional and cognitive status of older people who survived OHCA was usually lacking, and patient-important outcomes such as quality of life or independent living were seldom reported (1). As a consequence, even though this review shows the best available evidence to support the decision about resuscitation, its clinical use for geriatric patients with multimorbidity was limited because the primary studies did not address the predictive value of important factors such as mentioned above. Future studies should use uniform methods for reporting data and pre-arrest factors to increase the available evidence about pre-arrest factors on the chance of survival. Furthermore, patient-specific outcomes such as quality of life and post-arrest cognitive function should be investigated and reported too.

Paradoxically, while for many topics evidence of good quality regarding geriatric medicine is scarce, for some topics there is a wealth of literature; e.g. the various pharmacological interventions for dementia. A scoping review can provide oversight in topics for which much literature is available. We performed a scoping review about the pharmacological interventions for dementia. A scoping review generally discusses a broader research question than a systematic review and is able to map an area of research. Recently, it has

been shown that for two thirds of the meta-analyses published in 2010 there was at least one more additional meta-analysis available on the same topic. While some independent replication of meta-analyses may be useful, the huge number of double meta-analyses is a waste of efforts because they generally do not provide new information or evaluate important additional outcomes (14). This is illustrated by the fact that in our scoping review, most included systematic reviews were available about Alzheimer's disease with the outcomes cognition and behavioral problems, whereas few reviews addressed patient-centered outcomes and harms and burdens of therapies. Better coordination, communication between reviewers, and potentially registration of protocols for systematic reviews are options to consider (15;16). Furthermore, it is worthwhile to investigate in methods that reduce the labor of updating existing systematic reviews instead of writing new systematic reviews on the same topic from scratch (17).

Interpreting the evidence domain

Looking into more detail at the topic of assessing if the available evidence is applicable to older patients (1), the important issue of assessing the time-to-benefit (TTB) of an intervention is not often paid attention to (18). The TTB is the length of time needed to accrue an observable, clinically meaningful risk difference for a specific outcome (1). Especially in the older population, it is possible that the benefits of a treatment do not outweigh the expected life expectancy (19). Instead of discussing results only as differences of effect or number needed to treat (NNT), the TTB of an intervention should be reported. In chapter 6, we presented a novel method to define the TTB with the help of statistical process control (SPC)(20). This is an understandable and easy to understand and to perform method to get insight in the moment at which the effects between two groups start to differ. If this method would be reported in randomized controlled trials (RCTs), it immediately becomes clear what the time-to-benefit of a therapy is; in this way better targeting the investigated therapy to the individual patient and his living conditions and circumstances including life expectancy becomes possible.

Some clinicians believe that the importance of CPGs for patients with multimorbidity is limited (21); instead, individual treatment plans should be made. Although it is, of course, not possible to study the effect of interventions for all kinds of combinations of multimorbidity and to include this in CPGs, better tailoring CPGs to older people with multimorbidity remains an important issue in order to reduce variation and arbitrariness in practice, as well as to improve the quality of care (12;21-23). Several options have been mentioned to tackle this challenge. An option would be to incorporate as much as possible multimorbidity in guidelines by using cross references between the available recommendations in current guidelines so that possible conflicting recommendations can be identified. However, it is doubtful whether this is helpful, because adhering to all recommendations would often result in complex treatment regimens with multiple medications and conflicting side effects (12). In addition, for these cross-references a sophisticated digital environment is required which will not be available on the short term.

A second option could be to include much more detailed information on management of elderly patients, with a particular emphasis on eliciting patient and caregiver concerns, setting clinical priorities, managing expectations (particularly around prognosis), and fostering optimum communication. This will aid in making CPGs more patient-centered rather than disease driven (23). In the meantime, clinicians that treat these group of patients could rely on the guiding principles as proposed by the American Geriatrics Society (1). These guiding principles are: to elicit patient preferences, to appraise and to interpret available evidence with regard to its applicability to geriatric patients, to assess the patient's prognosis, to assess the clinical feasibility of a treatment and to optimize therapies and care plans (21). This approach should lead to patient-centered care, which is the best option as much evidence for geriatric care is currently lacking. In addition, multidisciplinary coordination and communication between healthcare professionals are important to adequately address multimorbidity (1).

Alternative ways for creating scientific evidence in the elderly

In order to improve EBM in clinical geriatric practice, the search for alternative ways to create evidence for this population should be continued. When performing a systematic review about a geriatric topics, many difficulties are encountered (24). Usually, the studied populations are heterogeneous, the included studies have different aims; often, no consistent categorization scheme for interventions is used and intervention details are minimally reported. Several of these problems can be overcome by performing an analysis of individual patient data (IPD) (25;26). We believe that this promising approach will generate high quality evidence targeted at older patients (27;28). Although criticasters state that older patients with multimorbidity and multiple impairments are rarely included in the original trials, we still believe that IPD reviews add valuable information, since by combining the sparsely included older patients out of different trials, evidence can be obtained without starting new studies. Analysis of individual patient data not only offers the possibility to perform analyses in subgroups for age, it also becomes possible to perform a time-to-event analysis, by including data that are collected after publication of the original trials, and to get more information about patient characteristics than usually described in the original trial reports. To illustrate this, we performed an overview of available IPD reviews that included (a subgroup of) older patients, which showed that in 50% of the cases the investigated effect differed between the younger and older groups (chapter 7). Therefore, it can be concluded that performing IPD reviews is relevant to get evidence specific for the elderly population, as the effect is different in the older groups.

In MEDLINE, we found relatively few IPD reviews concerning older people. IPD reviews are complex undertakings that require an existing infrastructure for sharing and analyzing data from different trials. We believe that investment in collaborations (between trialists, systematic reviewers, and guideline groups) to support IPD meta-analyses to answer questions about how best to address complex care needs of the older populations should be part of the future research agenda (24).

With respect to the desired study design for assessing the effect of an intervention, the RCT is rated as the strongest and most reliable research design that is currently available. However, relatively few RCTs are available for the geriatric population and many RCTs exclude older people, especially when they have comorbidities (29;30). This is illustrated by our overview of RCTs that investigated the effect of pharmacological treatments for delirium (chapter 8). We showed that 16 of 31 included studies excluded patients with cognitive impairment, although they are at high risk for developing delirium.

In order to increase the relevance of EBM to older persons, performing RCTs that predominantly enroll older patients might be part of the solution. We performed an RCT to assess the efficacy of acetaminophen on self-reported sleep problems (chapter 9). In our small sample we did not find evidence for an effect of acetaminophen on sleep problems in older people. Despite the measures we took to increase the chance of enrolling sufficient participants, such as using simple questionnaires, reducing the visits to the hospital and frequent phone contacts (31;32), we were unable to include sufficient patients. In our small sample we did not find evidence for an effect of acetaminophen on sleep problems in older people. Among the visitors of the outpatient clinic many were patients ineligible because of cognitive impairment. However, many potentially eligible patients did not give their consent. To get more clarity about the barriers and facilitators for older people toward participation in a randomized controlled trial, we investigated those reasons in the MAPLE trial (chapter 10) (33). We showed that the most frequently encountered barriers were the expected burden, the performing of extra blood tests and the taking of study medication (30;34).

We would advise researchers who are planning to perform a trial among geriatric patients to start with a pilot to explore the feasibility of the study and to put effort in a study design that yields the least possible burden for participants. Strategies to prevent missing data include selecting a primary outcome that is easy to determine and devising valid alternate definitions, adapting data collection to the special needs of the target population, pilot testing data collection plans, and monitoring missing data rates during the study and adapting data collection procedures as needed (35).

Given the efforts that are needed to perform an RCT among elderly patients, the low applicability and the often disappointing results, one should search for alternatives to RCTs to create evidence specific for this group. Alternative research designs could be n=1 studies; these are double-blind randomized trials in which a single patient undergoes a series of pairs of treatments, consisting of one active and one placebo or alternative treatment per pair, with the order determined by random allocation (36). An n=1 study is only possible for reversible outcomes such as pain and sleep disturbance. Another alternative is comparative effectiveness research (CER) because this explores comparisons of clinical approaches (37;38). An example of CER is the performance of pragmatic trials, in which the effectiveness of an intervention is measured in routine clinical practice (37), for example by comparing two different treatments that are used in real-life practice in a randomized way (39). Furthermore, evidence relevant for geriatric medicine could be

achieved from cohort studies of well-documented geriatric populations from which retrospective comparisons are possible. Another advantage of this design is that data collection is easier to perform and cheaper.
In order to perform research with older people successfully, in all cases simple measurements are needed and studies should be designed in a way that reduces the burden for participants as much as possible.

Recommendations for improving evidence-based geriatrics

In this thesis, we have shown that there are multiple ways to improve EBM in clinical geriatric practice. Searching for literature more efficiently could help to answer clinical questions more easily, and summarizing the available evidence in scoping reviews may simplify searching. In guidelines, more emphasis should be put on the applicability of the information to older and geriatric patients. The collaborative sharing of raw data from individual studies should be promoted and facilitated to improve evidence-based decisions in the growing population of older and more vulnerable patients in our society. In addition, clinical trials should be developed that improve the participation of representative older people and describe outcomes that are relevant to older people, taking into account what the most frequent barriers and motivators of a geriatric population are towards participation in clinical research. Furthermore, the body of evidence should be increased by applying alternative designs for RCTs (1).
All these measures should lead to an increased evidence-base for our growing population of older patients, thereby enabling evidence-based practice in geriatric medicine.

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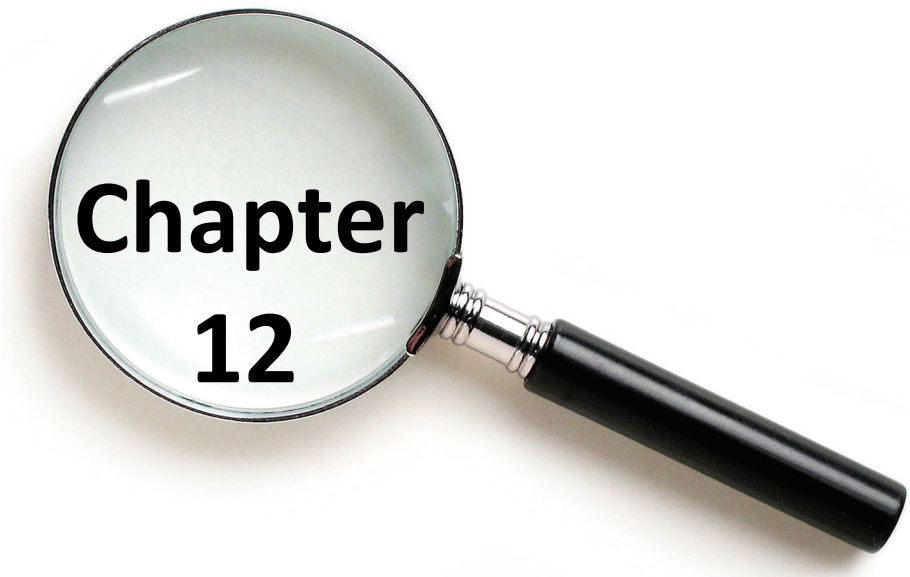


Summary in English

Summary

With an ageing population and increased life expectancy, the care and treatment of older people are a high burden on health care provision. With increasing age, the number of chronic diseases increases as well. Evidence-based medicine (EBM) is defined as the conscientious, explicit and judicious use of current best evidence in combination with the physician's experience and preferences, the patients' preferences and situation, in making decisions about the care of individual patients. Evidence specifically tailored to older people with multimorbidity is scarce because they are underrepresented in practically all medical research. However, creating evidence for this group is important because providing optimal care should be based on sound evidence.

The general aim of this thesis was to find ways to make the available evidence more accessible to clinicians and to develop opportunities to improve the use of EBM for geriatric medicine. In addition, we aimed to create evidence tailored to geriatric patients by summarizing individual patient data and by performing a randomized controlled trial. The first part of this thesis consisted of literature research.

In **Chapter 1**, the concept of EBM is introduced, especially with concern to its use in geriatric clinical practice, and the outline of this thesis is presented. In **Chapters 2 and 3**, we present our search filters that were developed to simplify efficient searching in MEDLINE for relevant literature concerning geriatric medicine. Search filters consist of MeSH terms and text words in titles and abstracts that are related to the subject of the intended search. With our search strategy or 'filter' focused on geriatrics, searching for relevant literature concerning geriatric medicine is simplified, thereby contributing to a better evidence-based practice. We developed specific and sensitive filters; the specific filter is especially useful to the clinician who wants to find a quick answer to a clinical question (specificity 96.6%); the sensitive search filter is useful to the researcher who wants to find as many relevant articles as possible (sensitivity 94.8%) without retrieving too many irrelevant articles. In **Chapter 3** we tested our search filters by investigating if they were able to retrieve the references that were identified by students of a postdoctoral course. This research showed that both the sensitive filter identified >85% of the articles considered relevant for daily clinical practice by young geriatricians from all over Europe; the specific filer identified more than 60%. This implies that physicians involved in elderly care can be confident that the majority of relevant articles for daily practice will be retrieved by using the filter in their literature searches.

Chapters 4 and 5 cover two different methods to summarize available literature on a specific topic reliably and systematically. **Chapter 4** systematically reviews what the pre-arrest predictors of survival are after cardiopulmonary resuscitation (CPR) from out-of-hospital cardiac arrest in an older population. In total, 23 studies were included; there was substantial clinical and statistical heterogeneity. 16 studies were of adequate methodological quality and sufficiently homogeneous to pool the reported percentage survival to discharge (4.1% (95% Confidence Interval (CI) 3.0-5.6%). We concluded that evidence for the predictive value of comorbidities and for the predictive value of age on

quality of life of survivors is scarce. Several studies showed that increasing age was significantly associated with worse survival, but the predictive value of comorbidity was investigated in only one study. In another study, nursing home residency was independently associated with decreased chances of survival. Only a few small studies showed that age is negatively associated with a good quality of life of survivors. We were unable to perform a meta-analysis of possible predictors due to a wide variety in reporting and statistical methods. Cohort studies of the predictors of survival of CPR with consistent reporting of the statistical methods and results of studies would facilitate the undertaking of a meta-analysis. This would provide useful information for prognostication for elderly. As quality of life and cognitive and functional status are even more important at older age than survival per se, these outcomes should be reported too in future studies about CPR. This would help both doctors and patients in decision-making about the desirability of cardiopulmonary resuscitation.

Chapter 5 describes a scoping review of systematic reviews that address pharmacological treatment of dementia. A scoping review is an overview that systematically reviews an extensive body of literature that addresses a broad research question. A scoping review 'maps' the relevant literature in a complete field of interest and describes only the main findings; by doing so, gaps in the available literature can be identified easily. In addition, we consulted a team of experts in the field to comment on the findings. For many current treatments, especially the efficacy of cholinesterase inhibitors for cognitive decline in Alzheimer's disease there is sufficient evidence. In conclusion, new research should focus on symptomatic treatment of the earliest and most salient complaints in AD, and on disease-modifying interventions acting at the level of the amyloid cascade.

In **Chapter 6**, we investigated whether patients with cognitive impairment were included in studies on pharmacological prophylaxis or treatment of delirium. Of the 3,476 participants of the 31 included studies, only 8% (n=274) were patients that were cognitively impaired. This hampers the generalizability of the results of these trials, because this group especially is at risk for developing delirium. These findings illustrate that results of clinical research are often not easily applicable to the geriatric population.

Results from intervention studies cannot always easily be applied to geriatric patients with limited life expectancy. Therefore, it is important to know what the time-to-benefit (TTB) of medication is. **Chapter 7** describes a novel method to estimate the time-to-benefit for preventive drugs with the Statistical Process Control (SPC). SPC is a statistical method that is used for monitoring processes for quality control. We used SPC to discriminate between normal variation over time in difference in number of fractures of placebo group and alendronate group and variation that was attributable to alendronate. Results are plotted in a graph that shows abnormal variation in difference in number of fractures directly. With this method, we showed that the time-to-benefit of alendronate in preventing fractures was 11 months for the total study group. In patients aged 70 years and above, the TTB was even shorter (8 months). SPC is a clear and understandable graphical method to determine the TTB; graphs show clearly at which moment a difference occurs between

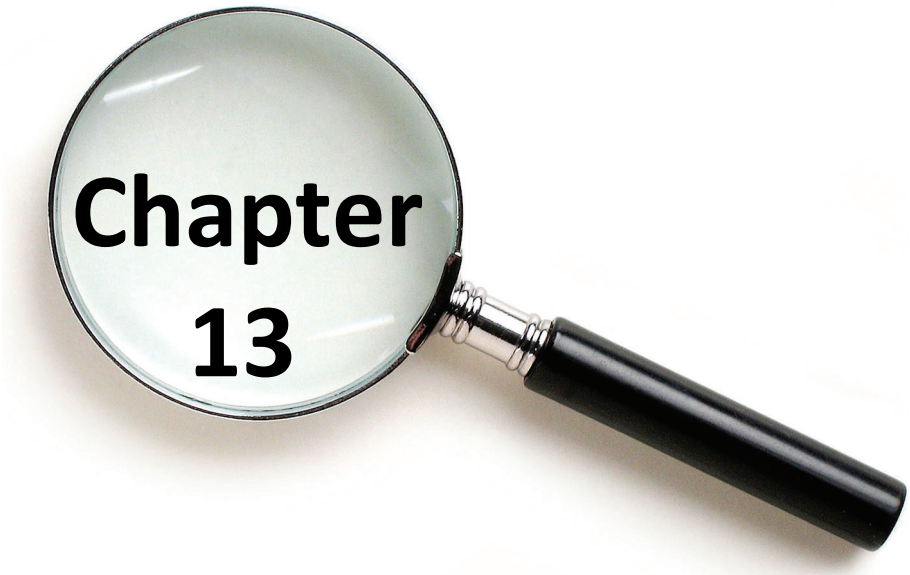
two groups, there is no need to define a pre-specified time point. We would encourage scientists to report the TTB, especially in studies for preventive medication in older patients. Clinical decision-making can be made more evidence-based by applying the TTB and the absolute risk reduction so that the pros and cons of initiating or stopping medication can be weighed for an individual patient with limited life expectancy.

In the second part of this thesis, we investigated ways to create evidence for geriatric patients. Meta-analysis and review of individual patient data (IPD) is a promising way of getting evidence for this group. Because the sparsely included older people in original trials are combined into a database and analyzed, evidence can be achieved without starting up new randomized controlled trials **(Chapter 8).** A MEDLINE search was conducted for IPD reviews of randomized controlled trials published before July 2012. 26 IPD reviews that described a subgroup of older individuals were included, and eight reviews with only older individuals. 14 IPD reviews suggested that older people should receive distinct treatments compared to younger people due to differences in effectiveness, whereof six reviews indicated that the investigated treatment(s) should be avoided in older patients. Because the included IPD showed that treatment effects frequently differed between older and younger patients, the relevance of this method for generating evidence in older patients is proved. Still, the application of IPD results to geriatric patients should be done cautiously, as they are often excluded from primary trials.

In **Chapter 9** the ASLEEP study, a randomized, placebo-controlled trial (RCT) that investigated the efficacy of acetaminophen in self-reported sleep problems was described. We included 61 individuals aged 65 years or older, either visitors of geriatric outpatient clinics or responders to advertisements in local papers. In our small sample, we did not find an effect of acetaminophen, but older people who use acetaminophen as an over-the-counter drug and feel they benefit from its use can safely continue this. Unfortunately, we did not succeed in enrolling the intended number of patients. In addition, we investigated the barriers and facilitators toward participation in a RCT **(Chapter 10)**. We evaluated the data of 195 participants and 92 non-participants of the Maple-study, a placebo-controlled RCT on the efficacy of melatonin for the prevention of delirium in elderly hip fracture patients. The most important facilitators to participate were a positive attitude toward research in general, the belief that this study was useful, and altruism. The most important barriers were the performance of the blood test, the use of extra medication and the expected burden in general. Surprisingly, the majority of the participants also considered the blood test useful.

The general discussion in **Chapter 11** elaborates on the observed results and offers directions for future research. In conclusion, this thesis demonstrated that there are multiple ways to improve EBM in clinical geriatric practice. Searching for literature more efficiently could help to answer clinical questions more easily, and summarizing the available evidence in scoping reviews may simplify searching and help identifying gaps in knowledge systematically. In guidelines, more emphasis should be put on the applicability

of the information to older and geriatric patients. The collaborative sharing of raw data from individual studies should be promoted and facilitated to improve evidence-based decisions in the growing population of older and more vulnerable patients in our society. In addition, clinical trials should be developed that improve the participation of representative older people and describe outcomes that are relevant to older people, taking into account what the most frequent barriers and motivators of a geriatric population are towards participation in clinical research. Furthermore, the body of evidence should be increased by applying alternative designs for RCTs. All these measures should lead to an increased evidence-base for our growing population of older patients, thereby enabling evidence-based practice in geriatric medicine.



Summary in Dutch
(Nederlandse samenvatting)

Nederlandse samenvatting

Het bieden van goede zorg aan ouderen is een uitdaging, omdat met het stijgen van de leeftijd het aantal ziektes en aandoeningen toeneemt. Evidence-based medicine (EBM) is 'het zorgvuldig, expliciet en oordeelkundig gebruikmaken van het best beschikbare bewijs bij het nemen van beslissingen over de zorg voor patiënten met inachtneming van de klinische expertise van de dokter, de situatie van de patiënt en de voorkeur van de patiënt en van de dokter'. Het is echter algemeen bekend dat ouderen worden uitgesloten van deelname aan wetenschappelijke studies, waardoor het toepassen van EBM in de klinische praktijk bemoeilijkt wordt. Ouderen worden soms uitgesloten op basis van leeftijdsgrenzen, vaak ook valt de oudere patiënt buiten de inclusiecriteria van een studie door bijvoorbeeld comorbiditeit. De algemene doelstelling van dit proefschrift was om te onderzoeken op welke manier meer resultaten uit wetenschappelijk onderzoek (wetenschappelijk bewijs of 'evidence') specifiek voor ouderen verkregen kan worden en hoe dat het beste door artsen die met ouderen werken in de klinische praktijk kan worden toegepast. Ook hebben zelf nieuwe evidence gecreëerd door het uitvoeren van een gerandomiseerde gecontroleerde studie (RCT) naar het effect van paracetamol op slaapproblemen bij ouderen.

Het eerste deel van het proefschrift gaat over het beter beschikbaar maken van resultaten uit wetenschappelijk onderzoek voor artsen en onderzoekers. Een belangrijke stap in EBM is het zoeken naar relevante wetenschappelijke literatuur die gebruikt kan worden bij het beantwoorden van vragen die in de klinische praktijk zijn ontstaan. Veel mensen vinden het echter moeilijk om efficiënt naar gepubliceerde artikelen te zoeken. In hoofdstuk 2 en 3 beschrijven we de ontwikkeling van zoekfilters die gebruikt kunnen worden om literatuur die relevant is voor ouderenzorg snel en gemakkelijk te vinden in MEDLINE, de meest gebruikte database om medische literatuur te vinden. Het ene zoekfilter was sensitief, wat wil zeggen dat dit filter zo veel mogelijk van de relevante literatuur vindt. Dit filter is geschikt voor onderzoekers die geen literatuur willen missen en zal ook veel ruis opleveren. Het andere filter is specifiek; het vindt niet alle relevante literatuur terug, maar zal ook weinig niet-relevante resultaten opleveren. Deze zoekfilters zijn getest onder studenten van een postacademische cursus en bleken ook daar goed te functioneren. Er bestaan zoekfilters voor allerlei onderwerpen, het blijkt dat deze nog weinig worden gebruikt door artsen, dit kan verbeterd worden door de bekendheid van zoekfilters te vergroten, bijvoorbeeld in het onderwijs, en door zoekfilters in te bouwen in literatuurdatabases.

In de hoofdstukken 4 en 5 bespreken we verschillende manieren om resultaten uit wetenschappelijke onderzoeken op een systematische manier samen te vatten, zodanig dat de resultaten betrouwbaar worden weergegeven. Hoofdstuk 4 beschrijft een systematische literatuuroverzicht van onderzoeken naar de invloed van leeftijd en cognitieve en functionele status op de kans dat ouderen een reanimatie buiten het ziekenhuis in goede conditie overleven. Hoewel er veel over dit onderwerp gepubliceerd is, was het aantal studies van goede methodologische kwaliteit beperkt. Dit leidt mogelijk

tot vertekende resultaten. De gerapporteerde percentages overleving van de studies die ingesloten werden in dit literatuuroverzicht werden bij elkaar opgeteld in een meta-analyse. Niet alle studies konden meegenomen worden in deze meta-analyse, omdat de patiënten en de omstandigheden rondom de reanimatie onvoldoende overeenkwamen in de verschillende onderzoeken. Hoewel een hogere leeftijd wel geassocieerd is met een lagere overlevingskans, corrigeerden weinig studies voor de functionele en cognitieve status van de patiënten vóór de hartstilstand, zodat nog steeds niet duidelijk is of hogere leeftijd de kans op overlijden vermindert, of de conditie van de patiënt. Vanwege al deze conflicterende resultaten zijn grotere cohort studies nodig om de werkelijke kwaliteit van leven na reanimatie voor ouderen te bepalen. Deze studies zouden de statistische methoden consistent moeten rapporteren; dit zal het uitvoeren van een meta-analyse vergemakkelijken.

Ouderen worden uit veel studies uitgesloten. Voor sommige onderwerpen echter, zoals bijvoorbeeld dementie, zijn talloze studies beschikbaar, waardoor het moeilijk kan zijn het overzicht te bewaren. Hoofdstuk 5 is een scoping review die beoogde systematische reviews van goede kwaliteit over de medicamenteuze behandeling van dementie samen te vatten. Een scoping review is een systematisch overzicht van literatuur die beschikbaar is over een bepaald onderwerp. Hierdoor wordt duidelijk welke onderwerpen voldoende belicht zijn en voor welke onderwerpen nog meer onderzoek nodig is.

De meeste reviews gingen over de behandeling van cognitieve achteruitgang met cholinesteraseremmers, hierover is voldoende wetenschappelijk bewijs beschikbaar. Nieuw onderzoek zou zich moeten richten op vroege symptomen van dementie en daarnaast is meer onderzoek nodig naar middelen die het beloop van de ziekte kunnen veranderen op het niveau van de amyloid cascade.

Voor ouderen met een beperkte levensverwachting is het van belang om alleen die medicatie voor te schrijven waarvan ze waarschijnlijk zullen profiteren. Dit geldt met name voor medicatie met schadelijke bijwerkingen. In hoofdstuk 7 laten wij zien hoe met de Statistische Proces Controle (SPC) op eenvoudige en inzichtelijke wijze de time-to-benefit (TTB) van medicatie berekend kan worden. De TTB wordt gedefinieerd als de tijd die nodig is voordat een preventief medicijn effectief wordt in een bepaalde groep patiënten. Dit is gedaan aan met behulp van originele data van de Fracture Intervention Trial (FIT), een grote RCT die het effect van alendronaat op het vóórkomen van klinische fracturen bij postmenopauzale vrouwen onderzocht. De TTB van alendronaat op het voorkómen van fracturen was 11 maanden, in de groep van 70-jarigen en ouder was de TTB zelfs nog korter. Deze informatie kan gebruikt worden in de klinische praktijk om een medicamenteuze behandeling beter af te stemmen op de individuele patiënt.

Ouderen met cognitieve beperkingen lopen een verhoogd risico op het ontwikkelen van een delier. Uit het literatuuroverzicht van hoofdstuk 7 blijkt echter dat patiënten met cognitieve stoornissen sterk ondervertegenwoordigd zijn in RCT's die de medicamenteuze behandeling van delier onderzochten. Het is mogelijk dat de onderliggende pathofysiologische mechanismen voor het ontwikkelen van een delier anders zijn bij

patiënten met dementie dan bij patiënten zonder neurodegeneratie. Deze resultaten illustreren dat onderzoeksgegevens niet zonder meer van toepassing zijn op patiënten in de klinische praktijk.

In het tweede deel van dit proefschrift beschrijven we methoden om wetenschappelijk bewijs te krijgen specifiek voor geriatrische patiënten.

Veel studies includeren weinig ouderen en het opzetten van studies met alleen ouderen kan op praktische bezwaren stuiten. Het samenvoegen van de originele oftewel individuele patiënten data (IPD) in een review of meta-analyse biedt de mogelijkheid om een interventie of diagnostische vraag te onderzoeken met voldoende power. In hoofdstuk 8 laten we zien dat de IPD review een goede methode is om evidence te verkrijgen voor de behandeling van ouderen. Veertien van de 26 ingesloten IPD reviews toonden aan dat ouderen beter een andere behandeling kunnen krijgen dan jongeren, terwijl 6 IPD reviews aantoonden dat de onderzochte behandeling beter niet aan ouderen gegeven zou moeten worden. Om het uitvoeren van IPD reviews te vergemakkelijken is het van belang dat onderzoeksdata gemakkelijk gedeeld kunnen worden. Bij het aanschrijven van auteurs met het verzoek om individuele data te delen is het van belang om een goed protocol met duidelijke (nieuwe) vraagstellingen te hebben, evenals een goede methodologische aanpak en goed vastgelegde afspraken over het gebruik van data.

Hoofdstuk 9 beschrijft de bevindingen van een multicenter, dubbelblinde RCT die wij hebben uitgevoerd naar het effect van paracetamol op slaapproblemen bij ouderen. Eenenzestig patiënten van 65 jaar of ouder werden gerandomiseerd voor 1000 mg paracetamol danwel placebo gedurende een periode van twee weken. In deze kleine, heterogene groep bleek geen verschil te zijn in de mate van slaapproblemen tussen beide groepen. Helaas zijn er in deze studie onvoldoende patiënten ingesloten, ondanks verlenging van de studie. Daarom hebben we onderzocht wat de beweegredenen zijn van patiënten om wel of niet deel te nemen aan een wetenschappelijk onderzoek (RCT). Hoofdstuk 10 beschrijft de resultaten van een survey die gehouden is onder patiënten die wel en geen toestemming gaven voor deelname aan een RCT die het effect van melatonine op het voorkómen van een delier bij oudere heupfractuur patiënten onderzocht. De belangrijkste beweegredenen om deel te nemen aan een onderzoek waren altruïsme en de mogelijkheid dat de studie bij zou dragen aan de eigen gezondheid; de belangrijkste redenen om deelname te weigeren waren de verwachte belasting en het feit dat er een extra bloedtest werd uitgevoerd. Deze laatste bevinding was opvallend omdat het merendeel van de deelnemers de bloedtest juist als zinvol beschouwde.

Het laatste hoofdstuk bevat een beschouwing van het gehele proefschrift, en geeft richting voor toekomstig onderzoek. Het blijkt dat er meerdere manieren zijn om de toepassing van EBM in de geriatrie te verbeteren. Het zoeken naar literatuur kan efficiënter worden, wat helpt in het beantwoorden van klinische vragen. Daarnaast zorgt het samenvatten van bewijs in systematische reviews en scoping reviews voor overzicht en maakt het duidelijk op welke vlakken meer bewijs nodig is. Ruwe data zouden voor iedereen beschikbaar moeten komen, waardoor het makkelijker wordt om de gegevens

van oudere patiënten samen te voegen in een IPD review, zodat evidence verkregen kan worden voor deze groep. Wanneer er RCT's worden opgezet voor ouderen moet extra aandacht worden besteed aan de opzet zodat de kans dat de inclusie wordt gehaald hoog is. Voordat een trial wordt uitgevoerd zou een pilot gedaan moeten worden om de haalbaarheid van de studie vast te stellen. Tevens kan gezocht worden naar alternatieve designs voor RCT's.
Door deze maatregelen wordt de zorg en behandeling van ouderen meer gebaseerd op wetenschappelijk bewijs, hetgeen hopelijk zal bijdragen aan betere zorg voor deze groeiende groep.

Addendum

List of co-authors

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PhD Portfolio / Publications

PhD training

General courses

-	The AMC World of Science	2010
-	Scientific Writing in English for Publication	2010
-	Evidence Based Searching	2010
-	Practical Biostatistics	2011
-	BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2011
-	Clinical Epidemiology	2012
-	Evidence-based medicine in clinical practice	2012
-	Evidence-based development of guidelines (EBRO)	2012

Seminars, workshops and master classes

-	Weekly department seminars	2010-2013
-	Master Class by prof. Gordon Guyatt	2012
-	Master Class by prof. Drummond Rennie	2013

Oral presentations

-	Search filters for geriatrics. *WEON, IJmuiden, the Netherlands*	2011
-	Search filters for geriatrics. *Geriatriedagen, Den Bosch, the Netherlands.*	2012
-	Evidence-based medicine in geriatrics. *Submitted symposium, EUGMS, Brussels, Belgium*	2012
-	Reviews of Individual Patient Data are useful in geriatrics. *Geriatriedagen, Den Bosch, the Netherlands.*	2013
-	Time to benefit of preventive medication. *Geriatriedagen, Den Bosch, the Netherlands (2nd author).*	2013

Poster presentations

-	Pre-arrest predictors for survival after out-of-hospital resuscitation in the elderly. *Geriatriedagen, Den Bosch, the Netherlands.*	2012
-	Search filters for geriatrics. *The Cochrane Colloquium, Madrid, Spain.*	2012
-	Underrepresentation of patients with dementia in trials on therapeutic or prophylactic treatment of delirium. *EUGMS, Brussels, Belgium.*	2012
-	ASLEEP, a protocol of a randomized controlled trial. *Geriatriedagen, Den Bosch, the Netherlands*.	2013

Teaching and supervision

Tutoring, Mentoring

-	Teaching of residents in training for psychiatry	2013
-	Tutor in course EBM in clinical practice	2012;2013
-	Tutor prestudents	2013
-	Supervision bachelor and master students	04/2012-09/2013 & 01/2013-05/2013

Publications

1. **van de Glind EM,** Rhodius-Meester HF, Reitsma JB, Hooft L, van Munster BC. Reviews of individual patient data are useful for geriatrics: an overview of available IPD-reviews. J Am Geriatr Soc, accepted for publication, February 2014.
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Curriculum Vitae

Over de auteur

Esther van de Glind werd geboren op 9 november 1981 in Amersfoort. Na het doorlopen van de basisschool in Voorthuizen en de middelbare school in Barneveld startte ze in 2000 met de studie geneeskunde aan de Universiteit Leiden. Deze studie werd afgerond in 2006. Na te hebben gewerkt als arts-assistent verpleeghuisgeneeskunde en interne geneeskunde, begon ze in 2008 aan de opleiding tot klinisch geriater. Zij startte met de vooropleiding interne geneeskunde in het Medisch Centrum Haaglanden te Den Haag en vervolgde haar opleiding in het Slotervaartziekenhuis te Amsterdam voor de somatische geriatrie. In 2010 onderbrak ze haar opleiding voor een promotietraject in het AMC. Zij was lid van het bestuur van de jNVKG, de arts-assistentenafdeling van de Nederlandse Vereniging voor Klinische Geriatrie, en nam daarnaast deel aan opleidingsvisitaties. Sinds oktober 2013 is zij weer verder gegaan met haar opleiding tot klinisch geriater in het Slotervaartziekenhuis.
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