Hot topic in geriatric medicine

Are old patients not fit for clinical trials, or do clinical trials not fit to old patients? A survey in 35 pharmaceutical companies

G. Kolb a,*, P. Rehmann b, N. Karbe-Voigt b, B. Wöstmann b

a Department of Geriatrics, St. Bonifatius Hospital, Wilhelmstraße 13, 49808 Lingen (Ems), Germany
b Department of Prosthodontics, Justus-Liebig-University, Schlangenzahl 14, 35392 Gießen, Germany

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A B S T R A C T

Clinical data and evidence-based guidelines for prescriptions for older patients are rare, and older patients are often excluded from clinical trials. The aim of this study was to use a questionnaire to assess the interest of pharmaceutical companies in including patients over 70 years of age in relevant pharmaceutical clinical trials. Additionally, the use of geriatric assessment tools was assessed. Overall, 35 international pharmaceutical companies were selected to report all studies performed over a 10-year period (1999 to 2009), and a total of 26 studies reported by eight companies were evaluated. In 19.2% of the studies, older patients were included but not analyzed separately. In 53.9% of the studies, age was either considered as a covariate or analyzed in a subgroup analysis. Seven studies included only patients aged 70 years and older. However, geriatric assessment tools were only utilized in four studies. Older patients were sufficiently included and analyzed in only a minority of company-initiated pharmaceutical studies. Given current demographic changes, there is an urgent need to address this situation.

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1. Background

Older patients are generally underrepresented or even excluded [1–3] from clinical trials, especially in pharmaceutical studies. However, older patients often represent the most significant group of consumers of investigated drugs [2,4]. So even in their geriatric medicines strategy the European Medicines Agency (EMA) pointed out, that “older people are the main users of medications – not a minority or special population... therefore, legislative and regulatory frameworks must be designed to ensure that the use of newly approved medicines in the intended population is supported by relevant data on the benefit-risk balance” [5]. But, in the reality, clinical data and evidence-based guidelines for prescriptions for older patients are rare. Furthermore, the results from clinical trials in younger patients are not directly applicable to the treatment of older patients [6,7]. The prescription of drugs that have not been tested in older people may endanger the health of patients, as solid evidence with regard to drug efficacy and toxicity within the patient age group may be unavailable [6–9]. This statement is also true for over-the-counter drugs, as package leaflets normally do not state whether the drug was tested in older patients.

For various reasons, age is the most significant barrier to subject recruitment for clinical trials [4,6,8,10]. Older patients show a high prevalence of comorbidities, especially when they have chronic diseases, and tend to require continuous and extensive drug therapy [4,11]. This increases the risk of side effects, and complications should be expected. The higher prevalence of cognitive impairments further aggravates the recruitment of appropriate study participants. Other exclusion criteria that have been reported in previous studies include frailty, communication barriers, transportation difficulties due to physical disabilities, visual or hearing deficits (sensory deficits), low income, and a lack of social support [8,10,12].

Little information is available regarding how many older people have participated in clinical research. Even if older individuals are involved, a separate evaluation of the results in the older population or an analysis of age as a covariate is anything but standard.

Therefore, only small developments in the understanding of the need to include older patients in clinical studies have been seen, and there is significant room for improvement. To achieve the goals of an effective geriatric drug therapy, the drug and the study design need to be accurately tested [4,13].

The aim of this survey was to use a questionnaire to assess the interest of pharmaceutical companies in including patients older than 70 years in relevant pharmaceutical clinical trials; in cases in which older patients were specifically excluded, the survey aimed

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to identify the reasons for their exclusion. The survey also assessed the use of geriatric assessment tools.

2. Materials and methods

The major suppliers of drugs (95% of all drugs delivered) in our hospital consortium were selected for inclusion in this study. All but one of the 35 identified pharmaceutical companies are international companies. Questionnaires in English and German (Appendix 1) were sent to the national headquarters of the companies.

The companies were asked to report all studies worldwide performed over a 10-year period (1999–2009) and to identify each study by its study code, study phase (I–IV) and investigated chemical substance/drug. Patients aged 70 years and older were not generally excluded, but the companies were asked if the final eligibility for the study was based on the results of one or more geriatric assessments or solely on the patient’s numerical age.

The questionnaires were sent to the companies in January 2009. One reminder was sent in April 2009, and a second reminder was sent in August 2009 (Fig. 1).

The survey was carried out on behalf of the German umbrella organization of the gerontological and geriatric

societies (Dachverband der Gerontologischen und Geriatrischen Gesellschaften Deutschlands e. V. – DVGG).

3. Results

Of the 35 companies that were contacted, eight did not reply even after the second reminder. Four companies reported that they did not have the capacity to complete the questionnaire or were bound by confidentiality. Thirteen manufacturers reported that they did not perform relevant clinical trials during the period (1999 until 2009). The replies of two companies were inconsistent and therefore excluded from the evaluation.

Overall, 26 studies reported by eight companies were evaluated (Fig. 1). Two studies were still in the recruitment phase, 24 studies were already completed. In six cases the number of subjects included was not revealed, the remaining 18 studies comprised a total of 29,487 patients (mean 1638, min 12, max 5385). The study types reported are listed in Table 1. Five of the studies (19.2%) reported that older patients were included but not separately analyzed. Ten studies (38.5%) included a subgroup analysis of patients aged 65 to 75 years, and four studies (15.4%) treated age as a covariate. In seven studies (26.9%), no age distinction was needed because the trials focused primarily on a population aged 70 years and older. However, only two of the studies answered the question,
“Could different results be found for younger as opposed to older patients?” Notably, these two studies showed no significant differences in the efficiency and variation in the toxicity of drugs between old and young patients. Both studies used geriatric assessment tools.

Only four studies reported using rudimentary geriatric assessments (activities of daily living, ADL; Barthel-Index; and quality of life, QoL).

4. Discussion

The aging process involves gradual and continuous changes in various physiological, physical, social and biological functions of the human body. In particular, the decline of physiological functions in older patients may influence drug absorption, metabolism and pharmacodynamics [4,11]. Because metabolism is often prolonged in older patients, adverse drug reactions are more common and more serious in this population. Due to patients being prescribed multiple medications, drug interactions are more likely to occur and require special attention in pharmacotherapy [4,11]. In Germany, 50% of all prescribed drugs are administered to patients aged 65 years and older. On average, polypharmacy occurs in every patient in this age group, with patients using approximately two to five different medications each day. Only approximately 10% of these drugs have been specifically tested for use in older patients [4,11,14]. And on the other hand, Beers et al. [7] summarized in their evaluation of the product information of 53 recently approved medicines that they “do not sufficiently provide adequate information about older individuals”.

The systematic exclusion of older subjects from many clinical studies has been discussed in the literature. In their survey, Martin et al. “demonstrated that geriatric medicine expertise is underrepresented in national prescribing agencies of European countries, with 90% having neither committees nor policies relating to prescribing to older people, but 58% having such committees/polices for children. This deficiency is likely to contribute to the current situation where older people are still commonly excluded from clinical trials and the consequent undermining of the evidence base of pharmacological therapies for a key demographic group of those consuming medicines” [13].

A limited number of authors have addressed the underlying reasons for this systematic exclusion and have classified the exclusion criteria as strongly justified, potentially justified and poorly justified [8,15]. This exclusion criteria are for example age (often poorly justified), comorbidities and frailty, cognitive impairments, physical disabilities, drug use, hearing or visual impairments and communication barriers. The common exclusion criteria in clinical trials are only reasonable in terms of comorbidities in the older patient population and the resulting high rate of medication use. Those factors make a separate analysis of the effects and active components of a drug difficult to perform. However, several other factors are also complicated. Cherubini et al. classified the exclusion criteria found in the literature as justified or poorly justified [8], and Bugeja et al. found that up to one-third of all original research papers in major medical journals excluded older subjects without any justification [2].

Van Spall et al. categorized approximately 61.5% of all applied exclusion criteria as poorly justified, 47.2% as strongly justified and 15.9% as potentially justified [15]. Moreover, Van Spall et al. [15] stated that clinical trials that are sponsored by the pharmaceutical industry show higher rates of exclusion by age, medication use and comorbidities, which may reflect the real market situation. In general, clinical trials aim to present a representative and “neat” database that allows for reproducible study designs. Each deviation of an older subject group from the ideal subject group alleviates the force of expression of a clinical trial. A heterogeneous group of older patients can complicate study designs and lead to higher study costs; therefore, many patients are systematically excluded. Another problem for clinical trials is that older patients have lower compliance rates and higher mortality rates during follow-up care. Cherubini et al. reported that the inability of older patients to attend follow-up visits was the reason for their exclusion in many clinical trials [8]. Efficacy trials with a well-defined and homogeneous subject group can generally be smaller, shorter, more efficient and less expensive [15]. On the contrary, the heterogeneity of older subjects may reflect the real world. Thus, there is a need to minimize the number of exclusion criteria and abolish age limits.

Additionally, moral and ethical motives for exclusion need to be discussed. Demented patients or patients who are not fully able to enter into a contract are not ethically considered to be fit to join clinical trials. The number of people with dementia is dramatically increasing, so a discussion about ethical questions related to their exclusion from trials is necessary. Currently, approximately one million people in Germany are living with dementia, and this number is expected to double by the year 2050 [14]. Ethical questions tend to end in a dilemma and cannot be completely resolved. However, a regulatory framework may help by mandating the inclusion of older people or by ensuring that financial barriers to the participation of older subjects in trials are dismantled [12]. In this aspect especially “ethics research committees are in a strong position to influence research practice and to reduce unethical age discrimination” [16,17].

This study’s first aim was to analyze the criteria for excluding subjects over 70 years of age by sending a questionnaire to 35 pharmaceutical companies. Although these companies were selected based on their role as major suppliers of drugs in our hospital consortium (St. Bonifatius Hospitalgesellschaft, Germany), there is no reason to assume that they are not representative of major pharmaceutical companies. This even more as 95% of the drugs used for all indications in a typical clinical setting were delivered from these companies. Our intention when deciding on this study design instead of a conventional review was to get information also on those studies that for whatever reason may not have been published. We hypothesized that there might be a bias in the literature due to non-reported trials. However, we had counted on a higher scientific interest of the companies in their projects as now reflected in the low response rate. This was especially confusing in cases when the inclusion of old people in studies was known to the authors and when we received the answer “no capacities”.

Because the questionnaires were sent to company headquarters, the competence of the actual individual respondent is unknown which is clearly a shortcoming of the design selected. To attempt to address potential problems related to this aspect, only open-ended questions were used; we avoided using predefined answers so as to encourage the companies to forward the questionnaire to a person involved in clinical research. However, this strategy may have been one reason for the relatively low response rate even after two
reminders. In the PREDICT project in 2011, a significantly higher return rate of mailed questionnaires was observed. However, in contrast to our survey, the PREDICT project focused only on opinions and differences of opinion between EU countries on the inclusion of older patients in clinical trials, whereas we asked in detail for studies that had actually been performed [18]. These results may also reflect a persistently high level of indifference to the challenge of demographic changes and the fact that older patients represent the majority of drug consumers.

A limited number of studies reported using geriatric assessment tools. Rudimentary geriatric assessments, including the ADL, instrumental ADL and Mini-Mental Status Test (MMST), were only used in two studies. There was no justification given as to why this type of assessment was so rarely utilized, particularly in light of the well-known fact that numerical age alone is an insufficient discriminator variable [12].

5. Conclusion

Unfortunately, only a minority of company-initiated pharmaceutical studies of older patients were sufficiently included and analyzed in the present assessment. The fact that most conventional study protocols do not fit the conditions and needs of older patients must be recognized. Therefore, to reflect the demographic reality, there is an urgent need for age-adapted study designs.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix 1. Questionnaire (English version)

Answer to:
Vorstand des DVGG
z. H. Herrn Prof. Dr. Dr. Gerald F. Kolb
Bonifatius Hospital Lingen
Fachbereich Geriatrie
Wilhelmstraße 13
49808 Lingen
Fax: 0591/910 97 1501
Mail: gerald.kolb@bonifatius-lingen.de

Survey about studies elder Patients
(Bitte pro Studie jeweils eine gesonderte Seite verwenden)

Study

Study Code

Chemical Substance/Drug

Study Design

Inclusion of Pts. age ≥ 70
Yes/No
If yes – No. (n =) and % of total No. of Study Patients

There was a separate evaluation of the older patients
Yes/No
If yes – Different results compared with younger patients?
Yes/No
Have the patients been involved in a geriatric assessment?
Yes/No
If yes – Which Assessment Tools have been used?

Appendix 1. (Continued)

-Activities of daily living (ADL):
  - Barthel-index:
  - Instrumental Activities of Daily Living (IADL) by
    Lawton & Brody:
    Which others?
    Yes/No
    Yes/No
  - Others: –

-Mobility:
  - Timed up an go:
  - Tinetti:
  - Others:
    Yes/No
    Yes/No

-Cognition:
  - Mini-Mental Status Test according to Folstein
  - Dem Tect:
  - Clock completion Test
  - Others:
    Yes/No
    Yes/No

-Depression:
  - Depression Scale according to Yesavage:
  - Others:
    Yes/No

-Comorbidities:
  - Charlson-Score:
  - SIRS-Labs Sepsis Test “VVOO”
  - Others:
    Yes/No
    Yes/No

Geriatric assessment was not performed

Comments/free text

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