



D6.1a: Literature review

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D6.1 description

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Executive Summary:

The literature review presented here identifies that there are guidance documents available relating to the management of polypharmacy in only 5 of the 28 EU countries, with guidance documents from Scotland, Netherlands and Germany scoring the maximum on the AGREE II-GRS criteria for Quality. The review also reports the current status of polypharmacy according to the published academic literature.

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I. Background for Deliverable 6.1

According to the Description of Work, WP6 aimed to collect up-to-date information on current strategies employed across Europe in order to manage polypharmacy and adherence in elderly.

In order to obtain this aims, twofold exercises have been performed:

- a comprehensive review of recent European grey and published literature on strategies of polypharmacy and non-adherence management in elderly

II. Grey and published literature review

1. Introduction

1.1 Multimorbidity

Multimorbidity is defined by the World Health Organisation as ‘the co-occurrence of two or more chronic medical conditions in one person’ [1]. Epidemiological data indicate that multimorbidity increases markedly with age, being prevalent in almost two thirds of individuals aged 80 years and over [2,3]. On average, those with multimorbidities have at least three long-term conditions, with cardiovascular (87.7 % of individuals), metabolic (62.2 %) and rheumatoid (40.2%) being the three most common. There is a significant relationship between multimorbidities and the use of health services; multimorbidity is related positively to interaction with community based health services (twice as high as non-multimorbid), and hospitalisation (three times higher) [4]. Multimorbidities impact quality of life, being associated with multiple symptoms, disabilities such as cognitive impairments, limited activities of daily living and reduced mobility hence are major public health issues [5]. One consequence is high economic burden due to complex healthcare needs and frequent interaction with healthcare services [6].

1.2 Polypharmacy

While the United Nations (UN) refers to those aged 60 years and over as ‘older people’, most developed countries have accepted the chronological age of 65 years as the definition of an ‘older person’ [7]. Given advances in pharmacotherapy, older people are likely to be prescribed multiple medicines to manage their multimorbidities. Single disease state led evidence-based guidelines do not provide sufficient coverage of issues of multimorbidities or the effects of old age, with the cumulative impact of treatment recommendations often resulting in overwhelming medicines burden [8,9]. Furthermore, as life expectancy increases, not only will people take medicines for a longer period of time but may develop more conditions that have the potential to need treatment but for which there is limited evidence of efficacy in extremes of age.

There is a wealth of recent evidence on the prevalence of prescribing of multiple medicines in older people. Data originating in the United Kingdom (UK), published in 2014, highlighted that 20.8% of those with two clinical conditions were prescribed four to nine medicines, and 10.1% of patients ten or more medicines; in patients with six or more comorbidities, values were 47.7% and 41.7% respectively and these figures increase with age [10]. A recent analysis of prescribing trends in the United States (USA) found that, between 1999 and 2012, polypharmacy (defined as ≥ 5 prescription medicines) increased from 24% to 39% for those aged 65 and above [11]. While there may be variability across countries, a narrative literature review published in 2005 identified this is a widespread global issue [12].

Polypharmacy, the prescribing of multiple medicines, is considered to be ‘one of the greatest prescribing challenges’, increasing the likelihood of adverse drug events, drug interactions and contributing to non-adherence to medicines regimens [13]. Furthermore, polypharmacy impacts significantly health outcomes and healthcare resources. While traditionally polypharmacy has been classified in terms of the number of medicines (usually defined as the use of five or more medicines) [14], Patterson et al. suggested, as part of a Cochrane review in 2012 (later updated in 2014), that there should be a change in emphasis from ‘inappropriate

polypharmacy' (prescribing of multiple medicines which are either inappropriate or no longer indicated) to 'appropriate' or 'optimal polypharmacy' (appropriate prescribing of multiple medicines) [15-17].

1.3 Managing inappropriate polypharmacy

It is evident that inappropriate polypharmacy is a major concern, hence promoting appropriate polypharmacy at the point of medicines initiation or during medicines review is, therefore, of the utmost importance and deserves greater attention.

A systematic review reported by Patterson et al. aimed to determine which interventions, alone, or in combination, were effective in improving appropriate polypharmacy and reducing medicines-related problems in older people. The review findings were based upon ten papers, with the authors concluding that, while there is uncertainty about the elements of intervention that impact positively appropriate polypharmacy, pharmaceutical care appears to improve prescribing [16,17].

There are a number of tools which may assist in promoting appropriate prescribing in older people. A systematic review by Kaufmann et al. aimed to create a comprehensive and structured overview of existing tools to assess potentially inappropriate prescribing [18]. Findings identified 46 different tools, with variation in methodological aspects and a general lack of validation in clinical settings. While many might serve as useful aids to improve prescribing, each tool has its limitations, strengths and weaknesses, and most were specific to the region and context in which they were developed. These tools were categorised as explicit, implicit or mixed. While implicit criteria focus on clinician interpretation and are time consuming, explicit criteria are designed to be easily and effectively interpreted. They provide details of categories of medicines and associated prescribing indicators to enhance reliable treatment evaluation. The most widely used include Beers Criteria, STOPP-START and Laroche Criteria [19-21]. The authors concluded that this review could serve as a summary to assist readers in choosing a tool, either for research purposes or for daily practice [18].

There remains, however, the need to translate the research evidence to policies and guidance for practitioners managing inappropriate polypharmacy and promoting appropriate polypharmacy. Developing, implementing and sustaining change requires commitment and investment at all levels of healthcare systems. The emphasis of the remainder of this paper is on a detailed description of a Pan-European initiative, with emphasis on the policy driven management of inappropriate polypharmacy in Scotland. Although there is a clear evidence supporting the need for strategy to manage polypharmacy especially in elderlies (whose multimorbidity favours excessive medicines intake) the evidence supporting one particular strategy and showing its superiority over another is still missing. This systematic review addresses this issue and tries to systematically summarize current strategies on polypharmacy management in elderlies.

1.4 SIMPATHY - Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly,

Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly (SIMPATHY) is a project funded by the European Union's Health Programme (2014-2020) [22], which commenced in June 2015 and will be complete by summer of 2017.

The overarching aim of SIMPATHY is to stimulate and support innovation across the EU in the management of polypharmacy and adherence in the elderly, with specific focus on addressing inappropriate polypharmacy. There is much emphasis on translating evidence to practice impacting healthcare structures, processes and

patient outcomes (clinical, humanistic and economic). The consortium programme of work will provide case studies in a range of different environments, identifying the framework and politico-economic basis for an EU-wide benchmarking exercise. Furthermore, the development of contextualised change management approaches and tools will aid target stakeholders who can influence and implement the necessary changes. Carefully targeted and comprehensive dissemination and engagement activities will be deployed to stimulate and support the innovation necessary to address this major EU healthcare challenge.

Work streams comprise: a systematic review of the published and grey literature of identified policies and guidelines across the EU for promoting appropriate polypharmacy in older people; case studies of the management of polypharmacy in the consortium countries; a benchmarking survey, aiming to collect quantitative and qualitative data from across the EU to provide a picture of progress towards addressing the urgent challenges associated with polypharmacy; a Political, Economic, Sociocultural, Technological, Environmental and Legal (PESTEL) analysis [23] and analysis of the Strengths, Weaknesses, Opportunities and Threats (SWOT) relating to polypharmacy and adherence management in the consortium countries; and, validation of SIMPATHY findings through an EU-wide consensus (modified Delphi) study.

The remainder of this part of the deliverable focuses on the evidence derived from the literature review.

2. Review aim

Several published systematic literature reviews have focused on aspects of polypharmacy management. While these reviewed the peer-reviewed published literature, one limitation was the omission of grey literature. As one objective of SIMPATHY is to benchmark the current policies and practice guidelines regarding polypharmacy management in older people, a broader review including both published and grey literature was conducted.

The primary aim of this review was to summarise current strategies on polypharmacy management in older people. To achieve this aim, a comprehensive review of recent (publications dated: 01 January 2010 – 30 June 2015) published and grey literature on strategies of polypharmacy and non-adherence management in older people was performed.

This systematic review was not aimed at supporting the need for polypharmacy management strategy. It was also not devoted to find particular treatment or solution for polypharmacy. It was not aimed at patients as a general group, but only at elderlies. This systematic review was also not searching for recommendations but explicitly strategies or guidelines.

3. Methods

Because a search for published strategies to manage polypharmacy was the primary aim of the review, a comprehensive, multifaceted search strategy was devised to target publications outlining strategic guidance for addressing inappropriate polypharmacy (but not implementation of guidance) in clinical practice, healthcare systems or research. To be included in the review as published strategy to manage polypharmacy in elderlies, at least one major stated purpose had to be the development of policies or guidelines to improve at least one component of polypharmacy management in older people and had to specify explicitly the guidance. Publications that only made recommendations as a part of the conclusions were excluded. There were several methods employed for the search, including a targeted database search, online grey literature search, desk review, and contact with key stakeholders.

Database search

A database search was conducted on Medline (via PubMed), Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and The Cochrane Library, according to PRISMA-P 2015 guidelines [24]. Comprehensive search strings were developed, for example for Medline: (multimed*^[ti] OR "multiple medication"^[ti] OR polifarma*^[ti] OR polyfarma*^[ti] OR polimedicin*^[ti] OR polymedicin*^[ti] OR polipharma*^[ti] OR polypharma*^[ti] OR polipragma*^[ti] OR polypragma*^[ti] OR politerap*^[ti] OR polyterap*^[ti]) AND (elder*^[ti] OR old*^[ti] OR age*^[ti] OR geriatric*^[ti]). Papers which were formal guidelines, accepted by public body, implemented on broader scale, included algorithm for polypharmacy and adherence management were accepted for final review.

Grey literature search

An online search of the grey literature was performed in ten European countries (Germany, Greece, Italy, Northern Ireland, Poland, Portugal, Spain, Sweden, The Netherlands, Scotland) along with the general non-country-specific search (in English). The search strategy included all 24 combinations of keywords from the following two groups,

Group 1: multimedication, multiple medication, polymedicine, polypharmacy, polypragmasy, polytherapy

Group 2: aged, elder, geriatric, old

After translating for each country, and cross-checking that these translated keywords were applicable to the management of polypharmacy, a search was performed using the Google search engine.

The country-specific search was restricted to relevant country domain (i.e. .de for Germany, .gr for Greece, etc.). In order to allow for comparable results to be obtained, and avoid the effect of cookie files, the previous search history was disabled, and the 'private' or 'incognito' mode of the search enabled (wherever applicable). For each combination of keywords, the first ten results generated by the Google search (giving a total of up to 240) was registered in a dedicated spreadsheet, and analysed.

Guidance documents identified via other methods

The search was complemented with any guidance documents known to the SIMPATHY consortium, as well as those identified through targeted contact with local stakeholders (two physicians, two pharmacists, and one politician) in each country.

Data analysis

Guidance documents were entered into a dedicated spreadsheet and screened to remove duplicate. Titles and abstracts of each item were reviewed independently by two reviewers in each country who were fluent in the relevant language. Final eligibility to be included in the review was determined by screening of full texts.

Data extracted from relevant guidance documents was entered into a dedicated spreadsheet and quality rated using the AGREE II instrument (The Appraisal of Guidelines for Research & Evaluation) which has 23 items organised into domains of: scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; and editorial independence [25]. Each item was scored on a seven-point scale, independently by two individuals educated to doctoral level and with expertise in the field of polypharmacy. A score of one indicated an absence of information or that the concept was reported very poorly. A score of seven indicated that the quality of reporting was exceptional and all criteria were met. A score between two and six indicated that the reporting of the AGREE II item did not fully meet the criteria. The overall score was the median of the 23 item scores.

To broaden the search beyond the consortium countries, the search was also conducted in the US Agency for Healthcare Research and Quality National Guidelines Clearinghouse and also the Guidelines International Network [26,27].

4. Results

Database search

There were 444 hits, of which 214 duplicates were removed, 136 were excluded for not dealing with polypharmacy management in older people, and 11 for other reasons (e.g. type of publication such as opinion, case report). The full text review of 83 papers revealed only one document which fulfilled the eligibility criteria [32] (Figure II.3.1).

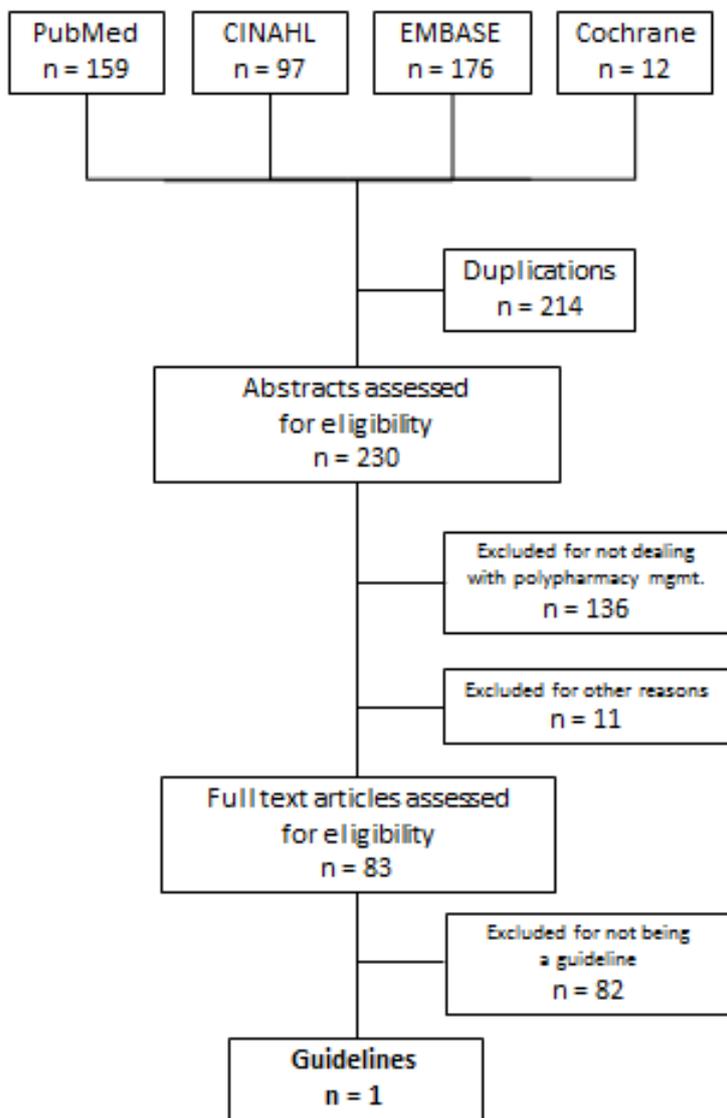


Figure II.3.1

Flow diagram of the published literature search.

Additional database search

A dedicated search in the Quality National Guidelines Clearinghouse and Guidelines International Network returned no results. The National Institute for Health and Care Excellence database search returned 25 results, of which only 1 was close to fulfilling search criteria, yet failed to fulfil them in full [53].

Grey literature search

The number of keyword combinations varied between countries, with a range of 3-24 due to issues in translation of keywords and applicability to the local literature on polypharmacy management. Furthermore, the Google search did not always retrieve the target number of ten. The total number of Google search results assessed against the eligibility criteria was 1705. Of these, 807 were excluded for not focusing on polypharmacy management in older people and 810 for the other reasons, usually not providing guidance. The full text of 88 items was reviewed, with ten fulfilling all criteria to be retained in the review. Full details are provided in Table II.3.1.

| Country | No. of keyword combinations used for the search (No. of individual keywords from Group 1 & 2) | No. of search results | Excluded after screening: | | No. of full text items assessed | No. of identified guidance documents fulfilling all criteria |
|-----------------------------|---|-----------------------|--|-------------------|---------------------------------|--|
| | | | For not dealing with polypharmacy management in older people | For other reasons | | |
| Germany | 24 (6 * 4) | 240 | 89 | 102 | 49 | 1 |
| Greece | 24 (6 * 4) | 179 [#] | 166 | 13 | 0 | 0 |
| Italy | 12 [§] (4 * 3) | 100 [#] | 46 | 47 | 7 | 0 |
| The Netherlands | 4 [§] (2 * 2) | 40 | 19 | 20 | 1 | 1 |
| Poland | 24 (6 * 4) | 233 [#] | 165 | 55 | 13 | 0 |
| Portugal | 24 (6 * 4) | 150 [#] | 113 | 29 | 8 | 0 |
| Sweden | 3 [§] (3 * 1) | 30 | 0 | 26 | 4 | 4 |
| Spain | 8 [§] (2 * 4) | 66 [#] | 2 | 63 | 1 | 0 |
| Scotland | 24 (6 * 4) | 240 | 156 | 80 | 4 | 4 |
| Northern Ireland | 24 (6 * 4) | 187 [#] | 21 | 165 | 1 | 0 |
| Non-country specific search | 24 (6 * 4) | 240 | 30 | 210 | 0 | 0 |
| Total | | 1705 | 807 | 810 | 88 | 10 |

Table II.3.1

Summary of the grey literature search. number of the keywords has been adjusted to the local language, # number of search results lower than the target due to some combination of keywords retrieving <10 results

Guidance documents identified through other methods

An additional 14 guidance documents were identified via other methods (i.e. desk review, and targeted contacts with local stakeholders), as shown in Table II.3.2.

| Country | No. of identified guidance documents |
|-----------------|--------------------------------------|
| Germany | 1 |
| Greece | 0 |
| Italy | 0 |
| The Netherlands | 4 |
| Poland | 0 |
| Portugal | 0 |
| Sweden | 4 |
| Spain | 1 |
| United Kingdom | 4 |
| Total | 14 |

Table II.3.2

Guidance documents identified through other methods

Integration and final list of identified guidelines

Combining the guidance documents derived from all sources and removing duplicates gave a final total of 19 documents from five countries (see Figure II.3.2), as listed in Table II.3.3, which also highlights quality according to the AGREE II-GRS criteria. The median overall score was 5, with a range of 3-7; three documents scored the maximum of seven, originating in Scotland, Germany and The Netherlands.



Figure II.3.2
Geographical distribution of identified guidance documents

| Guidance document details | Country of origin | Overall score according to AGREE II |
|---|-------------------|-------------------------------------|
| Regionala läkemedelsrådet i Uppsala-Örebroregionen. Behandlingsrekommendationer 2015. Läkemedelsbehandling av de mest sjuka äldre. Version 1.2: Updated March 2015 [28] | Sweden | 6 |
| Scottish Government Model of Care Polypharmacy Working Group. Polypharmacy Guidance (2nd edition). March 2015 [29] | Scotland | 7 |
| Västerbottens läns landsting. Terapirekommendationer, 2015 [30] | Sweden | 5 |
| Västra Götalandsregion. Äldre och läkemedel, 2015 [31] | Sweden | 4 |
| Bergert FW, Braun M, Ehrenthal K, et al. Recommendations for treating adult and geriatric patients on multimедication, 2014 [32] | Germany | 7 |
| Corrine Zara. Rational drug use. Medication management in the complex chronic patient: reconciliation, revision, deprescription and adherence, 2014 [33] | Spain | 5 |
| Ingrid Schubert, Hausärztlicher Leitliniengruppe Hessen und DEGAM. Hausärztliche Leitlinie „Multimedikation“, 2014 [34] | Germany | 5 |
| Midlöv P, Kragh A. Chapter: Läkemedelsbehandling hos äldre. In: Läkemedelsboken. Uppsala: Läkemedelsverket. 2014 [35] | Sweden | 3 |
| Verenso. Handreiking Geriatrisch assessment door de specialist ouderengeneeskunde. Utrecht: Verenso. 2014 [36] | The Netherlands | 3 |
| Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation: Making it safe and sound. The King's Fund. November 2013 [37] | England | 6 |
| Jones E. Polypharmacy: Guidance for Prescribing in Frail Adults. NHS Wales. May 2013 [38] | Wales | 5 |
| Nederlandse Vereniging voor Klinische Geriatrie. Richtlijn comprehensive geriatric assessment. Utrecht: Nederlandse Vereniging voor Klinische Geriatrie. 2013 [39] | The Netherlands | 5 |
| Socialstyrelsen. Läkemedelsgenomgångar för äldre ordinerade fem eller fler läkemedel. Stockholm: Socialstyrelsen. 2013 [40] | Sweden | 5 |
| Stockholms läns landsting. Äldre och läkemedel, 2013 [41] | Sweden | 5 |
| Nederlands Huisartsen Genootschap. Multidisciplinaire richtlijn Polyfarmacie bij ouderen 2012. Utrecht: Nederlands Huisartsen Genootschap. 2012 [42] | The Netherlands | 6 |
| NHS Greater Glasgow & Clyde. Mindful Prescribing Strategy – Polypharmacy. NHS. December 2012 [43] | Scotland | 6 |
| Melander A, Nilsson LG. Olämpliga listan - Koll på läkemedel, 2011 [44] | Sweden | 5 |
| Verenso. Multidisciplinaire richtlijn diabetes bij kwetsbare ouderen. Utrecht: Verenso. 2011 [45] | The Netherlands | 7 |
| Socialstyrelsen. Indikatorer för god läkemedelsterapi hos äldre. Stockholm: Socialstyrelsen. 2010 [46] | Sweden | 5 |

Table II.3.3

Guidance documents identified with AGREE II scores

Synthesis of search findings

The comprehensive and quality assured approaches employed in this literature review identified that only five EU countries have produced guidance documents which focus specifically on polypharmacy management in older people. In addition, only three of these were found to be fully satisfactory in terms of the AGREE II criteria. According to AGREE II partial evaluation German [32], Welsh [38] and Dutch [42] guidelines received the highest score in terms of scope, the lowest score was given to Swedish guideline [30]. In “Stakeholder involvement” domain the highest grade was given to Dutch [42, 45] and Scottish [43] guidance, while the lowest was received by Spanish [33]. For “Rigour of development” Dutch [45] was marked the best, with Spanish [33] and other Dutch [36] document having the lowest scores. German [32], English [37], Welsh [38] and Scottish [43] guidelines were awarded with highest grade for “Clarity of presentation”, with Swedish [40] having the most flaws in this domain. Applicability was the best in Scottish [29], but the poorest in Dutch [36]. Scottish [29, 43] and English [37] guidelines were assessed with highest marks for “Editorial independence” with Spanish [33] being at the opposite site.

Most of the identified guidance documents targeted elderlies, only few were devoted to polypharmacy in older people and also other groups of vulnerable people [32-34]. Two guidelines did not specify targeted population [30, 37]. All but one was generic (not specific to any single medical condition) [45]. Most paid attention to medicines selection at the point of prescribing (e.g. avoiding certain high-risk medicines, dose adjustment, and a ‘start low and go slow’ approach), and the need for regular review of medicines. Physicians and pharmacists were identified as key players, with a focus on multidisciplinary care and team working. Only seven guidance documents had any coverage of issues of non-adherence to medicines in older people [29, 32-34, 39, 42, 45]. In general, the guidelines were implemented on national level [35, 36, 39, 40, 42, 44-46], six were local [28, 30, 31, 33, 34, 41] and only one was international in scope [32]. In case of four documents, data on implementation was not available [29, 37, 38, 43].

The wider search identified further guidance documents from Australia [47-49], the US [50,51], and New Zealand [52]. After the search was concluded, a new guideline document has also been published by NICE in the UK [54].

Despite the comprehensive search and quality assurance approaches, there are several limitations to this review hence the findings should be interpreted with some caution. Grey literature searches are always limited in terms of retrieving all relevant literature. The search was restricted to Google and while this is the most widely used search engine, it is possible that not all guidance and policies were captured. In addition, it is highly likely that less widely used or disseminated policies and guidelines, such as those operating at local levels, were not retrieved. It is therefore important that those developing and implementing strategic approaches to the management of polypharmacy in older people disseminate widely.

Given the well-known consequences of inappropriate polypharmacy in older people, there is an urgent need to design, and implement evidence-based approaches throughout the EU. This aligns to the aims of SIMPATHY.

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