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Title:

Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus.

Running headline:

Clinical management of multimorbidity and polypharmacy.

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Abstract:

The complexity and heterogeneity of patients with multimorbidity and polypharmacy renders traditional disease-oriented guidelines often inadequate and complicates clinical decision making. To address this challenge, guidelines have been developed on multimorbidity or polypharmacy. To systematically analyze their recommendations, we conducted a systematic guideline review using the Ariadne principles for managing multimorbidity as analytical framework. The information synthesis included a multi-step consensus process involving 18 multi-disciplinary experts from seven countries. We included eight guidelines (four each on multimorbidity and polypharmacy) and extracted about 250 recommendations. The guideline addressed (1) the identification of the target population (risk factors); (2) the assessment of interacting conditions and treatments: medical history, clinical and psychosocial assessment including physiological status and frailty, reviews of medication and encounters with healthcare providers highlighting informational continuity; (3) the need to incorporate patient preferences and goal setting: eliciting preferences and expectations, the process of shared decision making in relation to treatment options and the level of involvement of patients and carers; (4) individualized management: guiding principles on optimization of treatment benefits over possible harms, treatment communication and the information content of medication/care plans; (5) monitoring and follow-up: strategies in care planning, self-management and medication-related aspects, communication with patients including safety instructions and adherence, coordination of care regarding referral and discharge management, medication appropriateness and safety concerns. The spectrum of clinical and self-management issues varied from guiding principles to specific recommendations and tools providing actionable support. The limited availability of reliable risk prediction models, feasible interventions of proven effectiveness and decision aids, and limited consensus on appropriate outcomes of care highlight major research deficits. An integrated approach to both multimorbidity and polypharmacy should be considered in future guidelines.

Key words: Multimorbidity [MeSH], Polypharmacy [MeSH], Patient-Centered Care [MeSH], Practice Guideline [MeSH], Continuity of Patient Care [MeSH], older adults

WORD count including text boxes: about 5,800 (max: 7,000) → 10…15% reduction → target word count 4,930 … 5,200 (now: 5,023 words)

Background:

Family physicians care for patients with multiple conditions, known as multimorbidity [1], in up to 80% of their consultations [2], while in geriatrics this is the case for essentially all patients. The presence of multiple conditions makes the patient's management challenging in a number of ways. First, the potentially complex interlinked pathophysiological pathways underlying the conditions need to be taken into account in diagnosis and monitoring. Secondly, when developing care plans for these patients, the potential risks and benefits of interventions need to be taken into account both for each condition and across diseases. Furthermore, some concurrent conditions may not necessarily have a clinical impact but may complicate interpretation of symptom presentations. All this makes the process more difficult and the outcomes less certain [3].

Patients with multiple conditions commonly take multiple prescriptions (polypharmacy) [4], which further increase complexity. Firstly, by increasing the potential for interactions between diseases and treatments medication choice is less straightforward. Secondly, by increasing the possibility that additional medications will be prescribed to counteract side effects prescribing cascades may occur. Physicians involved in caring for these patients report that current decision support is inadequate to optimize benefits and minimize harms in these patients with complex needs [5].

More than a decade ago, attention was drawn to the fact that the application of individual disease-oriented guidelines to patients with multimorbidity was not feasible and potentially harmful [6]. In addition to the potential harm from interactions between diseases and treatments, there is also an often unrecognized treatment burden [7, 8]. However, other studies indicate that adherence to clinical practice guidelines has the potential to improve outcomes for a range of chronic conditions including chronic heart failure and COPD, which commonly occur in people with multimorbidity [9-13].

Current approaches to support clinical decision making in multimorbidity and polypharmacy tend to adapt condition specific guidelines to take into account co-occurring problems; or to present principles on how to make a conscious use of disease oriented guidelines [14-16]. More recently, clinical practice guidelines for the management of multimorbidity and polypharmacy have been developed [17]. However, questions arise whether these guidelines provide relevant support for clinical decision making considering the vast heterogeneity of diseases, their potential combinations and varying degrees of disease severity in these patients.

We therefore aimed to identify and analyze available evidence-based clinical practice guidelines for multimorbidity or polypharmacy in order to investigate the clinical decision support they provide and the

key concepts they address. To facilitate the interpretation and actionability of the findings, we used the previously published Ariadne principles [15], which provide a framework to guide care delivery in patients with multimorbidity. At the core, the sharing of realistic treatment goals by physicians and patients results from i) an interaction assessment, i.e., the thorough assessment of diseases and treatments including their potential interactions, the patient's clinical status, their context as well as a consideration of treatment burden; ii) the prioritization of health problems taking into account the patient's preferences – his or her most and least desired outcomes; and iii) an individualized management plan which outlines the best options of care in diagnostics, treatment, and prevention to achieve the goals; iv) goal attainment is followed-up with a re-assessment in planned visits and v) the occurrence of new or changed conditions, such as an increase in severity, or a changed context may trigger a re-evaluation of the previous steps[15].

Methods:

We conducted a modified systematic guideline review [18] followed by a workshop-based consensus meeting with multidisciplinary experts from North America and Europe**.**

Literature Search and Selection

We conducted a systematic search for existing clinical practice guidelines in the electronic databases MEDLINE, The Cochrane Library, Health Services/Technology Assessment Texts (HSTAT), 'Turning Research Into Practice' (TRIP) and Guideline International Network (G-I-N) database, as well as in the National Guideline Clearinghouse combining controlled terms and free text words, such as comorbidity, multimorbidity, multiple conditions, polypharmacy, multiple drugs, multiple medications and older adults. We conducted the searches in February and March 2018, dated back to the database inception. In addition, we searched websites of guideline producing organizations including geriatric and primary care societies (the complete list is provided in **Web-Supplement 1**).

We included comprehensive guidelines or guideline-like documents on multimorbidity and polypharmacy, if they were "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [19], if their purpose was "to

make explicit recommendations with a definite intent to influence what clinicians do" [20] and if they were endorsed by guideline producing organizations or physicians' colleges. We accepted definitions of multimorbidity and polypharmacy used in individual guidelines and no language restriction was applied. We excluded disease-oriented guidelines (e.g., on osteoporosis management in elderly), guidelines with a narrow focus (e.g., on de-prescribing of potentially inappropriate medications in the elderly, using specific indicators such as Beers criteria [21]) or which did not report any methods of systematic development (a systematic literature search for at least some of the addressed questions had to be reported). Searches and selection of guidelines were conducted by two independent reviewers (AIGG and TSN).

Quality Appraisal

We (AIGG, MSB, JWB and TSN) appraised the quality of the guidelines using the MiChe Checklist [22, 23], which consists of eight specific questions (recommendations, audience, objectives, conflict of interest, systematic search, unambiguity, evaluation of benefits, and update) and two holistic items (overall assessment and recommendation for further use). Each specific question is answered as "Yes", "No" or "To some extent", the overall assessment is rated on a Likert scale ranging from "1"=very poor to "7"=very good, and the recommendation is rated with "Yes", "Yes, with certain reservations", and "No".

Data extraction

We (AIGG, CM, JWB, MSB, TSN) extracted data from the guidelines according to a pre-defined framework based on the Ariadne principles [15], which encompassed recommendations on (i) interaction assessment, (ii) prioritization of patient's preferences and agreement on shared treatment goals, (iii) individualized management of patients to achieve these goals and (iv) monitoring and follow-up of goal attainment. To fit the aim of the framework analysis, (v) ('trigger events' to (re)start the Ariadne principles) was reframed as methods for 'identification of the target population'.

Additional information on each guideline was extracted: the source, the year of publication, the country of origin, underlying concepts including definitions of multimorbidity and polypharmacy, the target setting, the target population and patient-related outcomes. For each topic of the a priori defined Ariadne framework, we (AIGG, CM, JWB, MSB, TSN) extracted the data into evidence tables using a standardized format, which included recommendation(s), level of evidence (LoE) and grade of recommendation (GoR) as provided in the guideline. When recommendations addressed more than one

domain of the framework, we (CM, JWB) agreed upon the domain that best matched the recommendation to avoid duplicates.

Analysis

The numbers of recommendations per topic and per guideline were described. We (AIGG, CM, JWB, SMS, TSN) conducted a thematic analysis, assigned categories and aggregated the recommendations as outlined above using the Ariadne framework.

Expert consensus process

We discussed the results of the thematic synthesis at a two-day meeting in May 2018. This meeting included a symposium, in which the background to the topic was elucidated and a workshop with 18 invited multidisciplinary experts – some of them with more than one area of expertise: geriatrics (7), primary care (6), public health and health services research (5), epidemiology (4) and pharmacy/pharmacology (2) from seven countries (Sweden (5), UK (4), USA (3), Italy and the Netherlands (2), Germany and Ireland (1)). The group discussion was audio-recorded and transcribed and served as triangulation of the thematic analysis. The results of the guideline review and the group discussion were agreed upon and synthetized by all authors.

Results:

In total, we included eight guidelines, four on multimorbidity and four on polypharmacy [24-31] (**Figure 1**; the list of excluded guidelines with reasons for exclusion is provided in **Web-Supplement 2**). Three guidelines were developed in the UK, two in Germany and one each in the US, the Netherlands and Mexico (**Table 1** [32, 33]). Four guidelines were of very good quality, the remaining had minor shortcomings - mainly due to a limited reporting quality, including two which did not report on update procedures and therefore scored lowest in that domain (for details of the quality appraisal see **Web-Supplement 3**).

In total, we extracted 246 recommendations (median: 27 recommendations per guideline (IQR: 13 to 52, range: 7-57)). The most common recommendations addressed the need for a thorough assessment of interactions and individualized management of patients (n=69 recommendations each), followed by identifying patient's preferences and goal setting (n=50), monitoring and follow-up (n=32), and identification of the target population (n=26) (**Figure 2**). Some of the recommendations were not specific to a single domain, for example, recommendations on individualized management also incorporated elements of monitoring and follow up.

[About here: Figure 1: Results of the search and selection process (flow chart)]

[About here: Table 1: Characteristics of included guidelines]

[About here: Figure 2: Distribution of recommendations per topic and guideline]

Identification of the target population

In one guideline, a systematic search for existing risk predicting models revealed many models for patients with multimorbidity but not for patients with polypharmacy [28]. This guideline recommended the identification of adults with multimorbidity at risk of adverse events (e.g., unplanned hospital admission or admission to a care home) using prognostic models – either opportunistically during routine care or proactively using the electronic medical record (EMR) [28]. Five guidelines provided information about risk factors for negative health outcomes covering different dimensions, such as condition-, medication-, adherence-related, and risks related to social context and health care utilization [25, 26, 28-30]. Condition-related risk factors included the presence of certain chronic diseases such as depression, dementia or cognitive decline, combinations of chronic mental and physical diseases such as diabetes and schizophrenia, the presence of conditions or events such as frailty, falls, non-specific symptoms and a worsening of health [25, 28-30]. Medication-related risks referred to drugs with a narrow therapeutic range, high potential for drug-drug interactions, the need for constant monitoring, psychotropic drugs and where patients received a suboptimal benefit from pharmaceutical treatment [26, 29]. Patients with non-adherence, difficulties managing their treatment regimen due to a high treatment burden or administration problems were also regarded as being at risk [25, 28, 29]. Social risk

factors included problems managing day-to-day activities, not living independently, limited ability to understand treatment recommendations (e.g., language problems and health literacy), advanced age and limited access to health care [25, 28-30]. The involvement of multiple and uncoordinated health care professionals and low uptake of care plans was noted to increase unplanned hospital admissions and emergency care [25, 28, 29].

Interaction assessment

According to the Ariadne Principles the interaction assessment should be conducted as a thorough assessment of diseases (including severity and impact on quality of life and functioning) and treatments (including potential interactions, adverse drug reactions, under-use and adherence), and of the clinical status and psychosocial context of the patient [15]. Seven guidelines addressed this principle, covering the medical history, a clinical and psychosocial assessment, a medication review and consideration of previous health services utilization [25-31]. Regarding the medical history, the documentation of all known diagnoses and conditions as well as existing laboratory test results and medication-related problems in the electronic medical record was recommended [25, 29]. One guideline [25] recommended the use of a structured questionnaire [34] about medication use, problems, experiences, worries and expectations. The clinical assessment included identification of a wide range of health problems as well as an assessment of physiological status and frailty [27, 28]. Recommendations on a medication review were at the core of the included polypharmacy guidelines, but were also addressed in the multimorbidity guidelines. One of them stressed the importance of informational continuity, in order to explore encounters with other physicians or health care professionals and changes in management over time [29] (**Textbox 1**).

[About here:

Textbox 1: Key recommendations on interaction assessment

Guiding principles

- Assess diseases, health problems, clinical and functional status, pharmacological and non-pharmacological treatment including potential interactions between diseases and treatments as well as the burden for the patient and take into account his/her psychosocial context [25-31].

- Involve patients and their family members or carers, where appropriate, in the assessment process, and clarify and resolve misconceptions [26, 31].
- Explore patient's contacts with other health care professionals and any related changes in management and consider using information technology support and a multidisciplinary team-based approach [26, 28, 29, 31].

Specific recommendations on clinical management

- **Clinical assessment**: Assess the management of health problems such as chronic pain, depression and anxiety, the presence of incontinence, the physiological and functional status and whether there are nutritional and hydration requirements [27, 28].
- **Medication review:** Evaluate the risk-benefit of each drug, its possible interactions and adverse effects, adherence to treatment and unmet needs and be aware of possible prescribing cascades [29, 30]. Assess the use of prescriptions, over-the-counter and food supplements or medicinal herbs and the actual implementation of a medication plan [29, 30]. Undertake a medication review regularly once a year; more often if needed, for example in relation to hospital stays: on admission, transfers between wards and at discharge [27, 29]. Use multiple methods such as health record reviews, patient surveys during consultations in practice or home visits and direct observation of medicines administration [26-29].

Specific recommendations on self-management support†

- Establish disease and treatment burden, its effect on day-to-day life including mental health, general wellbeing and quality of life [28]. Establish additional burden arising from caring responsibilities [27]. These features need to be incorporated when considering patients' capacity and the supports needed for self-management of long-term conditions and treatments [27].

Toolbox

Clinical assessment

- Instruments determining patient capacity and vulnerability to interactions, such as gait speed, self-reported health status, the PRISMA-7 questionnaire [35] (*primary care*), the 'Timed Up and Go' test [36], the Physical Activity Scale for the Elderly [37] (*hospital outpatients*) and Comprehensive Geriatric Assessment, CGA [38] (*hospitals*).

Medication assessment

- *Instruments based on implicit criteria*, such as MAI (Medication Appropriateness Index) [39], ACOVE (Assessing Care of Vulnerable Elders) [40], and the STRIP method (Systematic Tool to Reduce Inappropriate Prescribing) [28].

- *Instruments based on explicit criteria*, such as the STOPP (Screening Tool of Older Person's Prescriptions), START (Screening Tool to Alert doctors to Right Treatment) [41, 42], PIM lists (Potentially Inappropriate Medications, e.g., Beers criteria, EU-PIM list) [21, 43], FORTA (Fit for The Aged) [44-46], QT drug lists [47], databases on interactions, dosage adaption according to renal function and fall risk increasing drugs.

†We defined self-management support as the care and encouragement provided to people with chronic conditions and their families to help them understand their central role in managing their illness, make informed decision about care and engage in healthy behaviors (MacColl Center [50]).
End of Textbox 1]

Patient's preferences, prioritization and goal setting

All but one of the guidelines provided recommendations on eliciting patient preferences and expectations, including guidance on the level of involvement of patients and carers. The recommendations also focus on the process of shared decision making in relation to treatment options and the way they are communicated [24-29, 31]. Two guidelines provided specific recommendations regarding decision aids as tools to support shared decision-making [26, 28]. Additionally, one guideline referred to the need for specific skills and expertise in the use of patient decision aids [26] (**Textbox 2**).

[About here:

Textbox 2: Key recommendations on eliciting patient's preferences and sharing realistic treatment goals.

Guiding principles

- Patients should be encouraged to express their personal values, aims and priorities. The attitude of the patient regarding the treatment and its potential benefit has to be explored [26, 28, 31]. This includes addressing medical, psychological, emotional, social, personal, sexual, spiritual, cultural needs, vision, hearing and communication needs, environmental care needs and palliative and end of life care needs [24, 27].

Specific recommendations on clinical management

- Discuss with the person the purpose of the approach to care, for example, to improve quality of life and function. This might include reducing treatment burden and optimizing care and support by identifying possible improvements in medication and reducing inappropriate or medication with negative effect [28].
- The process of eliciting patient preferences requires several steps: 1) recognize when the patient with multimorbidity is facing a "preference sensitive" decision; 2) ensure patients with multimorbidity are adequately informed about the expected benefits and harms and 3) elicit patient preferences only after the individual with multimorbidity is sufficiently informed [24].
- Explore patient's expectations and objectives about treatments before prescribing [29].
- Find out what level of involvement in decision-making the person would like and avoid making assumptions about this [26].
- Use the best available evidence when making decisions with or for individuals, together with the clinical expertise and the person's values and preferences [26].

Specific recommendations on self-management support

- Encourage patients with multimorbidity to clarify what is important to them, including their personal goals, values and priorities [28].

Toolbox

- Use a patient decision aid to help them make a preference-sensitive decision that involves trade-offs between benefits and harms, if available in high quality and appropriate in the context of the consultation as a whole [26].

End of Textbox 2]

Individualized management

All guidelines provided recommendations on this topic. Guiding principles referred to the optimization of treatment benefits over possible harms in pharmaceutical and non-pharmaceutical interventions. They also referred to information that should be included in medication plans – and, in wider care plans, including social and tele-healthcare [24, 26-30]. Recommendations on treatment communication (with or without direct consideration of self-management support) was a strong focus in four guidelines [26-29] and the coordination of care was addressed in more than half of guidelines [24, 26-29, 31]. Self-management support was addressed indirectly in relation to individualized management in half of the

guidelines [26-29]. The guidelines which addressed this issue focused primarily on self-management support for medicines management and support with care coordination (**Textbox 3**).

[About here:

Textbox 3: Key recommendations on individualized management

Guiding principles

- Use strategies for choosing therapies that optimize benefit, minimize harm, and enhance quality of life for patients with multimorbidity and consider treatment burden, complexity and feasibility [24, 28].
- Consider the applicability and quality of evidence such as study population, study duration, benefits in terms of absolute risk reduction and time horizon. Studies in younger patients without multimorbidity and polypharmacy and with short follow-up times and relative risk reduction may overestimate benefits and underestimate harms, and time horizon to benefit may be too late to achieve relevant treatment effects in older patients with multimorbidity and polypharmacy [24, 28, 30].
- In deprescribing medication(s), follow a systematic approach including identification and prioritization of medicines to be discontinued, stopping one at a time and consideration of tapering dosage rather than stopping, and planning and communicating with patients (and caregivers, if necessary) [29].
- Ensure care plans are tailored to each person, giving them choice and control and recognizing the inter-related nature of multiple long-term conditions [27].
- Health professionals involved in the treatment of patients with multimorbidity should share relevant information about the person and their medicines – in particular when patients are transferred to another care setting [27, 31].

Specific recommendations on clinical management

- Be aware that the management of risk factors for future disease can be a major treatment burden for people with multimorbidity and should be carefully considered when optimizing care [28].
- When prescribing medications such as statins and bisphosphonates, be aware that they may only provide benefit to elderly patients who have estimated survival greater than five years [30].

- The selection of a primary pharmacy is recommended to support the coordination of self-administered drugs with regard to dosage instructions and overall medication regimens, particularly when there are multiple prescribers [29].
- Ensure there is community based multidisciplinary support for patients with multimorbidity with social care needs which might include, for example, a physiotherapist or occupational therapist, a mental health social worker or psychiatrist, and community based services [27].

Specific recommendations on self-management support

- Consider using an individualized patient-held medication plan that should include information on drugs and specific instruction for usage; if dosage is 'as needed', exact information about indication and individual dosage must be provided (single dose, interval and maximal daily dosage); in short-term prescriptions, the prospective end date should be specified and information about medication history and reduced renal function should be included when indicated [29].
- Develop care plans that address ongoing medical and social care needs for individual patients that focus on enhancing social connectedness and community involvement and also ensuring that carers' needs are taken into consideration and that these care plans do not add to treatment burden [26-28].
- Ensure ongoing and adequate communication, in particular around medicines and wider care plans with identification of perceived benefits and ensuring patient involvement in the process [26-28].
- Consider with the person whether there are tele-healthcare options that may support them to make informed choices to help them manage their conditions, as well as other potential benefits, risks and costs [27].
- Consider the use of named care coordinators who can agree a course of action with patients and their carers if these needs cannot be addressed by existing health and social care professionals. This may be particularly important at times of transition, for example when considering moving to a care home [27].

Toolbox

- Computerized decision support systems (CDSS) that support decision-making and prescribing but do not replace clinical judgment; and options for tele-healthcare [26, 27].

End of Textbox 3]

Monitoring and follow-up

In five guidelines, aspects of follow-up and monitoring of treatment effects as well as goal attainment were addressed [25-29]. Recommendations covered strategies in care planning, self-management and medication-related aspects, the communication with patients including patient information and safety instructions as well as adherence, the coordination of care regarding medication appropriateness and safety concerns, possible collaboration with pharmacies, the involvement of care coordinators, referrals and discharge management [25-29]. Additionally, organizational or health care professionals' responsibilities with regard to follow-up of medication-related aspects and the specific conditions in care homes were addressed in two guidelines [26, 27] (**Textbox 4**).

[About here:

Textbox 4: Key recommendations on monitoring and follow-up

Guiding principles

- Review and update medication / care plans regularly to recognize and record changes in needs [25-29].

Specific recommendations on clinical management

- Monitor treatment effects and clinical parameters, as well as side effects at follow-up appointments. Check for non-specific symptoms as potential indicators of complications resulting from treatment changes such as dry mouth, weakness / exhaustion / fatigue, drowsiness, reduced alertness, sleep disturbances, motor disorders, tremors, falls; constipation, diarrhea, incontinence, loss of appetite, nausea; skin rashes, itching; depression or lack of interest in usual activities, confusion (temporary or chronic), hallucinations, fear and agitation, vertigo, tinnitus and control clinical parameters (e.g., health examination, if necessary lab tests, ECG). Consider increasing the frequency of follow-up visits following treatment changes [29].
- Monitor treatment after discharge: due to the (usually) short duration of a hospital stay, newly introduced medications may not have reached steady state at discharge, because inpatient care is frequently shorter than 4 to 5 half-lives of prescribed drugs. Effectiveness and side effects cannot necessarily be properly assessed in hospital [29].
- Monitor ongoing treatment including demonstrations of medication administration (e.g., inhalers) and effective forms of self-monitoring [29].

- Consider continuing to offer information and support to people and their carers, even if they have declined this previously, recognizing that long−term conditions can be changeable or progressive, and people's information needs may change [26].

Specific recommendations on self-management support

- Review the self-management plan to ensure the person does not have problems using it [26].
- Health and social care providers should explain to patients, and their family members or carers where appropriate, how to identify and report medicines-related patient safety incidents that arise during follow-up periods [26].
- Self-management plans could include specific arrangements about follow-up to review the decisions made [28].

End of Textbox 4]

Discussion

Summary of included guidelines

Our review identified eight comprehensive guidelines addressing older patients with multimorbidity or polypharmacy. Many guidelines had to be excluded, mainly due to a lack of reporting of systematic search strategies. The vast majority of the included guidelines were of good quality according to the MiChe checklist [22, 23]. Interestingly, only three out of eight guidelines used levels of evidence and grades of recommendations, despite the recognition of their importance [48]. This may reflect the fact that evidence for effective interventions in this population is scarce and that expert consensus may often represent the best available evidence. However, this has also been the case for disease-specific guidelines. For example in chronic heart failure, a review found that about half of the guideline recommendations were consensus based [18]. There is a clear need to prioritize research to generate evidence for effective interventions in 'real world-patients'.

The recommendations included in the guidelines covered a broad spectrum of aspects related to clinical management and self-management and included recommendations beyond traditional realms of clinical guidelines (e.g., regarding structural requirements of organizations, knowledge and skills of different care providers). The recommendations varied in their specificity – from abstract guiding principles to detailed specific recommendations on necessary changes in practice and which tools may provide

actionable support. Multimorbidity guidelines more often provided generic guiding principles whereas those addressing polypharmacy tended to provide more specific recommendations and tools, but both remarkably neglected cognitive dysfunction. This is surprising for a frequent problem in this population, and one that is frequently underdiagnosed and has a major impact on health status and significant implications for self-management and interference with the health care system [49]. Furthermore, recommendations about pharmacologic treatment outweighed other types of recommendations (e.g. physical exercise) and no guideline specifically provided decision support for screening or diagnostic procedures. The impact of multimorbidity on diagnosis is not trivial as it can affect diagnostic accuracy and cause diagnostic delay with important implications for prognosis [50, 51].

The elicitation and consideration of patient preferences were considered as an essential part of the management of patients with multimorbidity and polypharmacy by all included guidelines. Caution was recommended in the use of decision aids because they were mainly developed for single diseases. It is noteworthy, that only three guidelines involved patient representatives in the development process.

Barriers and facilitators to implementation of recommendations - models of care

A major barrier to implementation is that current health care models are based on the single disease paradigm, with the exceptions of certain settings (primary care) and specialties services (geriatrics, mental health). Guideline recommendations generally did not account for settings, with the exception of differentiated recommendations on instruments that can assist a clinician in determining patient functional capacity. For example, the comprehensive geriatric assessment has been shown to be effective in hospitals [38] but not in primary care [52]. Geriatricians and family physicians, while sharing a holistic approach, typically operate under different frameworks. Geriatricians are more often based in hospitals and provide care for the 'geriatric patient', while family physicians provide longitudinal care for unselected patients [53-55]. This has important implications in primary care, for example, in the organization of long-term follow-up and monitoring but also in the identification of patients with multimorbidity and polypharmacy who are at risk of developing negative health outcomes – that is to differentiate between the 'fit and active' and people in need for an intensified care approach [28]. Research is needed that supports reliable methods for ensuring that those most at risk of adverse events are identified and benefit from appropriate interventions.

The complexities associated with the management of multimorbidity and polypharmacy make it advisable to ensure the involvement of other health and social care professionals for patients with low

health literacy or a complex social background. Multi-professional care teams including social workers – and in certain countries, care coordinators– may facilitate the implementation of recommendations if a context-specific tailoring of the recommendations is warranted.

Guidelines recommend clinicians to encourage self-management but the evidence for specific self-management support programs on multimorbidity is lacking [56]. Further research is needed on interventions that support priority setting and strategies to reduce barriers to self-management.

Communication with patients

All guidelines emphasized the importance of communication with patients and their carers about the patient's needs, priorities and preferences for improving patient-centered health outcomes and minimizing the burden of care and overtreatment. Decision aids to support this communication process have been developed generally for single chronic diseases. Decisions about health care for patients with multimorbidity require a more individualized approach that considers outcomes across conditions, such as overall health related quality of life, functioning or symptom-free survival.

Patient's preferences for prioritized outcomes may shift over time [57] but also with regard to the alternatives [58, 59]. Repeated communication about the importance and prioritization of outcomes is therefore imperative. Instruments to communicate about prioritization and preferences with regard to outcomes have been developed, again mostly with a condition specific approach [60-62] and limited psychometric properties [61]. Individual goal setting and prioritization are core tasks in individualizing the care for patients with multimorbidity. Although interventions have been developed to support this collaborative process between patients and clinicians, the evidence supporting their effectiveness is still lacking [56]. Which components of these often multi-faceted interventions are most relevant is not clear [63].

Guidelines on multimorbidity vs. polypharmacy

Existing guidelines follow concepts on multimorbidity (diagnosis based) or polypharmacy (treatment based) but the issues raised are relevant to essentially the same patient population in clinical practice. Medication reviews for example, were at the core of the polypharmacy and multimorbidity guidelines and the review itself must take into consideration both patient's conditions and treatments. The

separate production of guidelines addressing either multimorbidity or polypharmacy seems arbitrary and their combination would also relieve the burden – for developers and users.

Limitations

The systematic guideline review method offers a transparent and comprehensive approach to the analysis of existing guidelines, but our in-depth text analysis may not be free from subjectivity with regard to the themes selected and presented in this review.

Concluding remarks

Our review identified eight comprehensive guidelines of good quality addressing older patients with multimorbidity or polypharmacy. The guideline recommendations covered a broad spectrum of aspects of clinical and self-management, beyond the realms of traditional disease-oriented guidelines. The recommendations varied in their specificity – from abstract guiding principles to detailed recommendations on necessary changes in practice and tools providing actionable support. The limited availability of reliable risk prediction models, feasible interventions of proven effectiveness and decision aids, as well as limited consensus on appropriate outcomes of care highlight major research deficits. An integrated approach to both multimorbidity and polypharmacy should be considered in future guidelines.

Conflict of interest statement

The authors have nothing to disclose.

Authors' contributions:

Drs. CM, JMV and JWB designed the concept and the program for the workshop and agreed upon with all authors. Drs. CM and JWB had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. Drs. AIGG, CM, JWB, MSB and TSN extracted the data and assigned them to the Ariadne framework. Drs. AIGG, CM, JWB, SMS, MSB and TSN drafted the information synthesis. Drs. CM, JWB, SMS, MET, KJ and JMV led the workshop. Drs. CM, JWB, JMV,

SMS, AIGG, and MC drafted the first manuscript and all authors substantially contributed to the conception, acquisition, analysis and interpretation of data, revised the manuscript critically for important intellectual content, and finally approved it to be published.

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Figures, Tables and Web-Supplements

Figure 1: Results of the search and selection process (flow chart)

Figure 2: Distribution of recommendations per topic and guideline

Table 1: Characteristics of included guidelines

Legend: *Used in 2/8 recommendations; †King's Fund definitions: Appropriate polypharmacy - 'Prescribing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimized and where the medicines are prescribed according to best evidence'; Problematic polypharmacy - 'The prescribing of multiple [medicines] inappropriately, or where the intended benefit of the [medicines are] not realized'[33]; ‡Guiding principles for medicines optimization (the Royal Pharmaceutical Society): '(1) aim to understand the patient's experience, (2) evidence based choice of medicines, (3) ensure medicines use is as safe as possible, (4) make medicines optimization part of routine practice' [32]. Abbreviations: ADR – adverse drug reaction, GoR – grade of recommendation, LoE – level of evidence, MM – multimorbidity, PIM - potential inappropriate medication, PP – polypharmacy

Web-Supplement 1: search strategy and a complete list of web-sites visited

Web-Supplement 2: list of excluded guidelines with reason for exclusion

Web-Supplement 3: quality appraisal of included guidelines

Table 1: Characteristics of included guidelines

Name, publication year	Country of origin	Target setting	Underlying concept and definition	Target population	Outcomes addressed	Underlying frameworks	LoE / GoR
AGS 2012 [26]	U.S.A.	Primary care, (secondary care)	MM: multiple chronic conditions	Older patients with MM	Meaningful outcomes for older adults with MM (quality of life, physical function, independent living) and intermediate outcomes	5 domains: Patient Preferences, Interpreting the Evidence, Prognosis, Clinical Feasibility, and Optimizing Therapies and Care Plans	No
DEGAM 2017 [33]	Germany	Primary care	MM: ≥3 chronic diseases	Adult patients with MM	(Patient-centred care)	Meta-algorithm derived from N-of-1 guideline approach	Yes
IMSS 2013 [32]	Mexico	'Primary care, (secondary care)	PP: ≥4 medications	Older people with PP	Improvement in the quality of medical prescription in the elderly, preventing and detecting inappropriate prescription, reducing adverse drug events,	n.a.	Yes

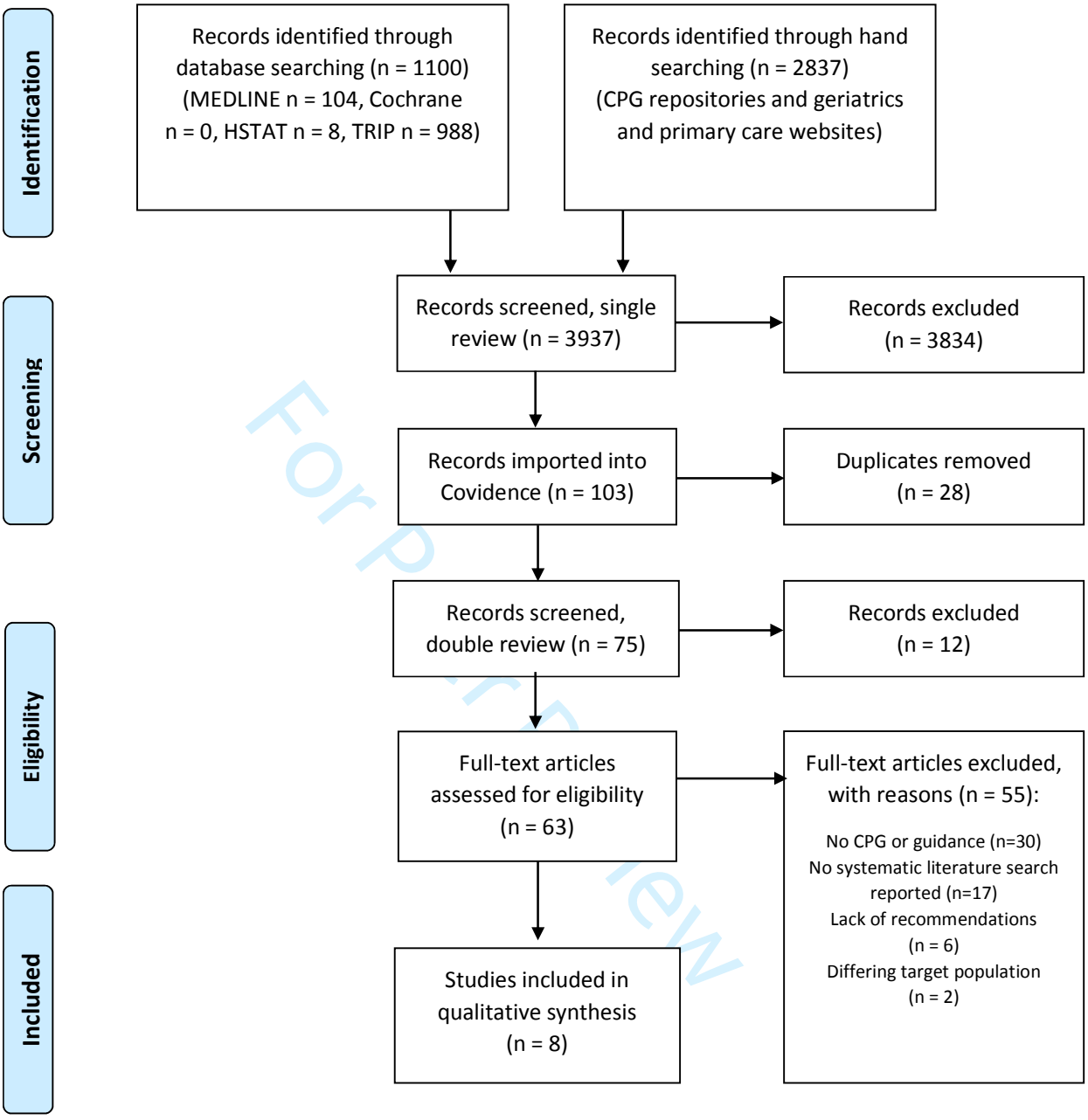
Name, publication year	Country of origin	Target setting	Underlying concept and definition	Target population	Outcomes addressed	Underlying frameworks	LoE / GoR
					deterioration of patients' health and the unjustified expense of means		
LLGH & pmv & DEGAM 2014 [31]	Germany	Primary care	PP: ≥5 chronic prescriptions	Adult patients with PP; excl.: palliative care	PIM and related ADR, underuse and misuse, treatment burden	Medication use process; Medication Appropriateness Index	No
NHG & NVKG & OMS 2012 [27]	Netherlands	Primary and secondary care	PP: ≥5 chronic prescriptions	Polypharmacy plus at least one risk factor: decreased kidney function; decreased cognitive function; increased fall risk; decreased compliance; living in an institution; unplanned hospital admission	Optimizing medication use; decrease medication-related problems; decrease medication-related hospital admissions	Systematic Tool to Reduce Inappropriate Prescribing (STRIP)	No*
NICE 2015a [28]	UK	Health and social care	PP: King's Fund definition[†]	People taking ≥1 medicines and their families and carers	Up to 8 pre-specified outcomes per review question (e.g. clinical	Guiding principles for medicines optimization (the	Yes

Name, publication year	Country of origin	Target setting	Underlying concept and definition	Target population	Outcomes addressed	Underlying frameworks	LoE / GoR
					outcomes, medicine-related outcomes and problems, health and social care utilization, planned and unplanned health services contacts, health and social care related quality of life, for example long-term harm, disability)	Royal Pharmaceutical Society)‡	
NICE 2015b [29]	UK	Health and social care	MM: ≥1 long-term condition (lasting ≥1 year and impacts on a person's life)	Older people with social care needs and multiple long-term conditions (including both physical and mental health conditions), and their carers.	No pre-specified outcomes, full consideration of a wide range of outcomes as reported in studies	n.a.	No
NICE 2016 [30]	UK	Primary and secondary care, more specialized services	MM: (1) the co-existence of ≥2 long term conditions; (2) the combination of 1 chronic disease	Adults (≥18 yrs.) with multimorbidity; people with multiple conditions where these present significant problems to everyday	To improve quality of life by promoting shared decisions based on what is important to each person in terms of treatments, health priorities,	n. a.	No

Name, publication year	Country of origin	Target setting	Underlying concept and definition	Target population	Outcomes addressed	Underlying frameworks	LoE / GoR
			with ≥1 other disease or bio psychosocial factor or somatic risk factor	functioning or where the management of their care has become burdensome to the patient and/or involves a number of services working in an uncoordinated way.	lifestyle and goals by means of by reducing treatment burden (polypharmacy and multiple appointments) and unplanned care		

Legend: *Used in 2/8 recommendations; †King's Fund definitions: Appropriate polypharmacy - 'Prescrib-ing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimized and where the medicines are prescribed according to best evidence'; Problem-atic polypharmacy - 'The prescribing of multiple [medicines] inappropriately, or where the intended benefit of the [medicines are] not realized'[35]; ‡Guiding principles for medicines optimization (the Royal Pharmaceutical Society): '(1) aim to understand the patient's experience, (2) evidence based choice of medicines, (3) ensure medicines use is as safe as possible, (4) make medicines optimization part of routine practice' [34]. Abbreviations: ADR – adverse drug reaction, GoR – grade of recommen-dation, LoE – level of evidence, MM – multimorbidity, PIM - potential inappropriate medication, PP – polypharmacy

Figure 1: Results of the search and selection process (flow chart)



	1. Identification of the target population	2. Interaction assessment	3. Patient's preferences, prioritization and goal setting	4. Individualized management	5. Monitoring and follow-up
AGS 2012 [26]			8	6	
DEGAM 2017 [33]		2	4	1	
IMSS 2013 [32]	2	11		4	
LLGH & pmv & DEGAM 2014 [31]	8	27	4	10	7
NHG & NVKG & OMS 2012 [27]	4	3	2		1
NICE 2015a [28]	2	8	22	10	8
NICE 2015b [29]		9	6	27	15
NICE 2016 [30]	10	9	6	11	1

Legend: polypharmacy guideline multimorbidity guideline

Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus.

Supplement 1

Table 1: List of databases and date of search

Abbreviation	Name, country and internet address	Date
Cochrane	Cochrane Library http://onlinelibrary.wiley.com/cochranelibrary/search/	2018-02-20
HSTAT	Health Services/Technology Assessment Texts https://www.ncbi.nlm.nih.gov/books/NBK16710/	2018-02-20
Medline	Medline http://www.pubmed.com	2018-02-20
TRIP	Trip Database www.tripdatabase.com	2018-02-20

Table 2: List of websites and organisations and dates of searches

Abbreviation	Name, country and internet address	Date
ACP	American College of Physicians (USA) https://www.acponline.org/clinical-information/guidelines	2018-02-10
AGS	American Geriatrics Society (USA) http://americangeriatrics.org	2018-02-10
AETMIS	Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (Canada) https://www.cadth.ca/aetmis	2018-02-10
AHFMR	Alberta Heritage Foundation for Medical Research (Canada) http://www.ahfmr.ab.ca/	2018-02-10
AHRQ (AHCPR)	Agency for Healthcare Research and Quality (USA) (formerly Agency for Health Care Policy and Research) http://www.ahrq.gov	2018-02-12
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft www.akdae.de	2018-03-29
AMA	Alberta Medical Association (Canada) http://www.albertadoctors.org/	2018-02-12
AMDA	American Medical Directors Association (The Society for post-acute and long-term care medicine) www.amda.com	2018-03-29
ANZSGM	Australian and New Zealand Society for Geriatric Medicine (Australia and New Zealand) http://www.anzsgm.org	2018-02-12
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften http://www.awmf.org/awmf-online-das-portal-der-wissenschaftlichen-medizin/awmf-aktuell.html	2018-02-14
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin http://www.aezq.de/	2018-02-10

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Abbreviation	Name, country and internet address	Date
BÄK	Bundesärztekammer www.baek.de	2018-03-29
BCC	British Columbia Council www.bcguidelines.ca	2018-03-29
BGS	British Society of Geriatrics (UK) http://www.bgs.org.uk	2018-02-12
BMA	British Medical Association www.bma.org	2018-03-29
CADTH	Canadian Agency for Drug and Technologies Assessment (Canada) http://www.cadth.ca	2018-02-12
CGS	Canadian Geriatric Society (Canada) http://www.canadiangeriatrics.ca	2018-02-12
CDHSH	Commonwealth Department of Human Services and Health (Australia) www.health.gov.au	2018-02-12
CEDIT	Comité d'Evaluation et de Diffusion des Innovations Technologiques (France) http://cedit.aphp.fr/category/hta-2/	2018-02-12
CMA	Canadian Medical Association www.cma.ca	2018-03-29
CFP	Canadian Family Physician (Canada) http://www.cfp.ca	2018-02-12
CTFPHC	Canadian Task Force on Preventive Health Care (Canada) http://www.ctfphc.org/	2018-02-12
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin www.degam.de	2018-02-14
Deprescribing	Deprescribing.org (Canada) http://www.deprescribing.org	2018-02-13
DGIM	Deutsche Gesellschaft für Innere Medizin www.dgim.de	2018-02-14
DGK	Deutsche Gesellschaft für Kardiologie www.dgk.org	2018-02-22
DIMDI	Deutsches Institut für Dokumentation und Information www.dimdi.de	2018-02-14
Duodecim	Leitlinienseite von The Finnish Medical Society Duodecim (Finland) https://www.duodecim.fi/english/duodecim/the-finnish-medical-society-duodecim/	2018-02-13

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Abbreviation	Name, country and internet address	Date
Evidence.de	Evidence.de www.evidence.de	2018-03-29
EUGMS	European Union Geriatric Medicine Society (European Union) http://www.eugms.org/publications/resources.html	2018-02-13
GAIN	Guidelines and Audit Implementation Network www.gain.org	2018-03-29
GIN	Guideline International Network http://www.g-i-n.net	2018-02-13
GR	Gezondheidsraad (Netherlands) http://www.gr.nl/	2018-02-13
GSA	The Gerontological Society of America (USA) http://geron.org	2018-02-13
GuiaSalud	Biblioteca de Guías de Práctica Clínica del Sistema Nacional de Salud (Spain) http://www.guiasalud.es	2018-02-13
Guideline Central	Guideline Central (USA) https://www.guidelinecentral.com/	2018-02-13
HealthTeamWorks	HealthTeamWorks www.healthteamworks.org	2018-03-29
HHS	Unites States Department of Health and Human Services (USA) http://www.hhs.gov	2018-02-13
ICSI	Institute for Clinical Systems Improvement (USA) http://www.icsi.org	2018-02-13
IMSANZ	Internal Medicine Society of Australia and New Zealand (Australia and New Zealand) https://www.imsanz.org.au/	2018-02-13
INAHTA	International Network of Agencies for HTA (the former international organization for health technology assessment, today HTAI – Health Technology Assessment International) http://www.inahta.org	2018-02-13
ITA	Institut für Technikfolgen-Abschätzung (Austria) https://www.oeaw.ac.at/itahome/	2018-02-13
KBV	Kassenärztliche Bundesvereinigung www.kbv.de	2018-02-14
MCRC	Multiple Chronic Conditions Resource Center http://multiplechronicconditions.org/#MCC	2018-04-16
MJA	Medical Journal of Australia www.mja.com.au	2018-03-29
MOH	Ministry of Health Singapore www.moh.giv.sg	2018-03-29

Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus.

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Abbreviation	Name, country and internet address	Date
MSAC	Medical Services Advisory Committee (Australia) http://www.msac.gov.au/	2018-02-13
NGC	National Guideline Clearinghouse (USA) https://www.guideline.gov/search?q=polypharmacy+OR+%22multiple+drugs%22+OR+multimedication+OR+multimorbidity+OR+%22multiple+conditions%22+OR+comorbidity&pageSize=100&page=1	2018-02-13
NHMRC	National Health Medical Research Council www.nhmrc.org.au	2018-03-29
NHS	National Health Services (UK) http://www.nhs.uk	2018-02-13
NHS QIS	NHS Quality Improvement Scotland (UK) http://www.nhshealthquality.org/nhsqis/nhsqis_sub_publications.jsp	2018-02-13
NICE	National Institute for Clinical Excellence (UK) http://www.nice.org.uk/	2018-02-13
NSW Health	New South Wales Health www.nih.gov	2018-03-29
NQMC	National Quality Measures Clearinghouse (USA) http://www.qualitymeasures.ahrq.gov	2018-02-13
NZGG	New Zealand Guideline Group (New Zealand) https://www.health.govt.nz/publications?f%5B0%5D=im_field_publication_type%3A26	2018-02-13
NZHTA	New Zealand Health Technology Assessment (New Zealand) http://www.otago.ac.nz/christchurch/research/nzhta/	2018-02-12
REDETS	Red Española de Agencia de Evaluación de Tecnologías (Spain) http://www.redets.msssi.gob.es/	2018-02-12
SBU	The Swedish Council on Technology Assessment in Health Care (Sweden) http://www.sbu.se/en/publications/	2018-02-12
SEGG	Sociedad Española de Geriatría y Gerontología (Spain) http://www.segg.es	2018-02-12
SEMI	Sociedad Española de Medicina Interna (Spain) http://www.fesemi.org	2018-02-12
semFyC	Sociedad Española de Medicina Familiar y Comunitaria (Spain) http://www.semfyc.es	2018-02-12
Sign	Scottish Intercollegiate Guidelines Network www.sign.ac.uk	2018-03-29
SGIM	Society of General Internal Medicine (USA) http://www.sgim.org	2018-02-12

Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus.

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Abbreviation	Name, country and internet address	Date
TA-SWISS	Zentrum für Technikfolgenabschätzung (Switzerland), https://www.ta-swiss.ch/en/	2018-02-12
TNO	Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek (Netherland) http://www.tno.nl/homepage.html	2018-02-12
USPSTF	US Preventive Task Force (USA) https://www.uspreventiveservicestaskforce.org/	2018-02-12
VATAP	VA Technology Assessment Program, Department of Veterans Affairs (USA) https://www.healthquality.va.gov/	2018-02-12
WHO	World Health Organization	2018-03-29
ZonMw	Netherlands Organization for Health Research and Development (Netherlands) http://www.zonmw.nl/index.asp?s=4535	2018-02-12

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Supplement 2

List of excluded guidelines with reason

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Supplement 3

Table 1: Quality appraisal of included guidelines

MiChe items / ***Guidelines***	1. Identification of key recommendations and comprehensibleness	2. Specification of the guideline's target audiences and scope	3. Specification of the objectives and the target population	4. Independence and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguity of recommendations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommendation for further use
AGS 2012 [26]	2	1	1	1	1	2	2	3	6	1
DEGAM 2017 [33]	1	1	1	2	2	1	2	1	6	1
IMSS 2013 [32]	1	1	1	1	1	2	1	3	5	2
LLGH & pmv & DEGAM 2014 [31]	1	1	1	1	1	1	1	1	7	1
NHG & NVKG & OMS 2012 [27]	1	1	1	1	1	1	1	1	7	1
NICE 2015a [28]	1	1	1	1	1	1	1	1	7	1
NICE 2015b [29]	1	1	1	1	1	1	1	1	6	1
NICE 2016 [30]	1	1	1	1	1	2	1	2	6	1

Article type: Review - **JIM-18-0656-R21** (~~first~~ second revision)

Title:

Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus.

Running headline:

Clinical management of multimorbidity and polypharmacy.

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Abstract:

The complexity and heterogeneity of patients with multimorbidity and polypharmacy renders traditional disease-oriented guidelines often inadequate and complicates clinical decision making. To address this challenge, guidelines have been developed on multimorbidity or polypharmacy. To systematically analyze their recommendations, we conducted a systematic guideline review using the Ariadne principles for managing multimorbidity as analytical framework. The information synthesis included a multi-step consensus process involving 18 multi-disciplinary experts from seven countries. We included eight guidelines (four each on multimorbidity and polypharmacy) and extracted about 250 recommendations. The guideline addressed (1) the identification of the target population (risk factors); (2) the assessment of interacting conditions and treatments: medical history, clinical and psychosocial assessment including physiological status and frailty, reviews of medication and encounters with healthcare providers highlighting informational continuity; (3) the need to incorporate patient preferences and goal setting: eliciting preferences and expectations, the process of shared decision making in relation to treatment options and the level of involvement of patients and carers; (4) individualized management: guiding principles on optimization of treatment benefits over possible harms, treatment communication and the information content of medication/care plans; (5) monitoring and follow-up: strategies in care planning, self-management and medication-related aspects, communication with patients including safety instructions and adherence, coordination of care regarding referral and discharge management, medication appropriateness and safety concerns. The spectrum of clinical and self-management issues varied from guiding principles to specific recommendations and tools providing actionable support. The limited availability of reliable risk prediction models, feasible interventions of proven effectiveness and decision aids, and limited consensus on appropriate outcomes of care highlight major research deficits. An integrated approach to both multimorbidity and polypharmacy should be considered in future guidelines.

Key words: Multimorbidity [MeSH], Polypharmacy [MeSH], Patient-Centered Care [MeSH], Practice Guideline [MeSH], Continuity of Patient Care [MeSH], older adults

WORD count including text boxes: about 5,800 (max: 7,000) → 10…15% reduction → target word count 4,930 … 5,200 (now: 5,023 words)

Background:

Family physicians care for patients with multiple conditions, known as multimorbidity [1] ~~(see also review 1 [ref] in this issue)~~, in up to 80% of their consultations [2], while in geriatrics this is the case for essentially all patients. The presence of multiple conditions makes the patient's management challenging in a number of ways. First, the potentially complex interlinked pathophysiological pathways underlying the conditions need to be taken into account in diagnosis and monitoring. Secondly, when developing care plans for these patients, the potential risks and benefits of interventions need to be taken into account both for each condition and across diseases. Furthermore, some concurrent conditions may not necessarily have a clinical impact but may complicate interpretation of symptom presentations. All this makes the process more difficult and the outcomes less certain [3].

Patients with multiple conditions commonly take multiple prescriptions (polypharmacy) [4], which further increase complexity. Firstly, by increasing the potential for interactions between diseases and treatments medication choice is less straightforward. Secondly, by increasing the possibility that additional medications will be prescribed to counteract side effects prescribing cascades may occur. Physicians involved in caring for these patients report that current decision support is inadequate to optimize benefits and minimize harms in these patients with complex needs [5].

More than a decade ago, attention was drawn to the fact that the application of individual disease-oriented guidelines to patients with multimorbidity was not feasible and potentially harmful [6]. In addition to the potential harm from interactions between diseases and treatments, there is also an often unrecognized treatment burden [7, 8]. However, other studies indicate that adherence to clinical practice guidelines has the potential to improve outcomes for a range of chronic conditions including chronic heart failure and COPD, which commonly occur in people with multimorbidity [9-13].

Current approaches to support clinical decision making in multimorbidity and polypharmacy tend to adapt condition specific guidelines to take into account co-occurring problems; or to present principles on how to make a conscious use of disease oriented guidelines [14-16]. More recently, clinical practice guidelines for the management of multimorbidity and polypharmacy have been developed [17]. However, questions arise whether these guidelines provide relevant support for clinical decision making considering the vast heterogeneity of diseases, their potential combinations and varying degrees of disease severity in these patients.

We therefore aimed to identify and analyze available evidence-based clinical practice guidelines for multimorbidity or polypharmacy in order to investigate the clinical decision support they provide and the

key concepts they address. To facilitate the interpretation and actionability of the findings, we used the previously published Ariadne principles [15], which provide a framework to guide care delivery in patients with multimorbidity. At the core, the sharing of realistic treatment goals by physicians and patients results from i) an interaction assessment, i.e., the thorough assessment of diseases and treatments including their potential interactions, the patient's clinical status, their context as well as a consideration of treatment burden; ii) the prioritization of health problems taking into account the patient's preferences – his or her most and least desired outcomes; and iii) an individualized management plan which outlines the best options of care in diagnostics, treatment, and prevention to achieve the goals; iv) goal attainment is followed-up with a re-assessment in planned visits and v) the occurrence of new or changed conditions, such as an increase in severity, or a changed context may trigger a re-evaluation of the previous steps[15].

Methods:

We conducted a modified systematic guideline review [18] followed by a workshop-based consensus meeting with multidisciplinary experts from North America and Europe**.**

Literature Search and Selection

We conducted a systematic search for existing clinical practice guidelines in the electronic databases MEDLINE, The Cochrane Library, Health Services/Technology Assessment Texts (HSTAT), 'Turning Research Into Practice' (TRIP) and Guideline International Network (G-I-N) database, as well as in the National Guideline Clearinghouse combining controlled terms and free text words, such as comorbidity, multimorbidity, multiple conditions, polypharmacy, multiple drugs, multiple medications and older adults. We conducted the searches in February and March 2018, dated back to the database inception. In addition, we searched websites of guideline producing organizations including geriatric and primary care societies (the complete list is provided in **Web-Supplement 1**).

We included comprehensive guidelines or guideline-like documents on multimorbidity and polypharmacy, if they were "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [19], if their purpose was "to

make explicit recommendations with a definite intent to influence what clinicians do" [20] and if they were endorsed by guideline producing organizations or physicians' colleges. We accepted definitions of multimorbidity and polypharmacy used in individual guidelines and no language restriction was applied. We excluded disease-oriented guidelines (e.g., on osteoporosis management in elderly), guidelines with a narrow focus (e.g., on de-prescribing of potentially inappropriate medications in the elderly, using specific indicators such as Beers criteria [21]) or which did not report any methods of systematic development (a systematic literature search for at least some of the addressed questions had to be reported). Searches and selection of guidelines were conducted by two independent reviewers (AIGG and TSN).

Quality Appraisal

We (AIGG, MSB, JWB and TSN) appraised the quality of the guidelines using the MiChe Checklist [22, 23], which consists of eight specific questions (recommendations, audience, objectives, conflict of interest, systematic search, unambiguity, evaluation of benefits, and update) and two holistic items (overall assessment and recommendation for further use). Each specific question is answered as "Yes", "No" or "To some extent", the overall assessment is rated on a Likert scale ranging from "1"=very poor to "7"=very good, and the recommendation is rated with "Yes", "Yes, with certain reservations", and "No".

Data extraction

We (AIGG, CM, JWB, MSB, TSN) extracted data from the guidelines according to a pre-defined framework based on the Ariadne principles [15], which encompassed recommendations on (i) interaction assessment, (ii) prioritization of patient's preferences and agreement on shared treatment goals, (iii) individualized management of patients to achieve these goals and (iv) monitoring and follow-up of goal attainment. To fit the aim of the framework analysis, (v) ('trigger events' to (re)start the Ariadne principles) was reframed as methods for 'identification of the target population'.

Additional information on each guideline was extracted: the source, the year of publication, the country of origin, underlying concepts including definitions of multimorbidity and polypharmacy, the target setting, the target population and patient-related outcomes. For each topic of the a priori defined Ariadne framework, we (AIGG, CM, JWB, MSB, TSN) extracted the data into evidence tables using a standardized format, which included recommendation(s), level of evidence (LoE) and grade of recommendation (GoR) as provided in the guideline. When recommendations addressed more than one

domain of the framework, we (CM, JWB) agreed upon the domain that best matched the recommendation to avoid duplicates.

Analysis

The numbers of recommendations per topic and per guideline were described. We (AIGG, CM, JWB, SMS, TSN) conducted a thematic analysis, assigned categories and aggregated the recommendations as outlined above using the Ariadne framework.

Expert consensus process

We discussed the results of the thematic synthesis at a two-day meeting in May 2018. This meeting included a symposium, in which the background to the topic was elucidated and a workshop with 18 invited multidisciplinary experts – some of them with more than one area of expertise: geriatrics (7), primary care (6), public health and health services research (5), epidemiology (4) and pharmacy/pharmacology (2) from seven countries (Sweden (5), UK (4), USA (3), Italy and the Netherlands (2), Germany and Ireland (1)~~; see **Web-Supplement 2**~~). The group discussion was audio-recorded and transcribed and served as triangulation of the thematic analysis. The results of the guideline review and the group discussion were agreed upon and synthetized by all authors.

Results:

In total, we included eight guidelines, four on multimorbidity and four on polypharmacy [24-31] (**Figure 1**; the list of excluded guidelines with reasons for exclusion is provided in **Web-Supplement 2~~3~~**). Three guidelines were developed in the UK, two in Germany and one each in the US, the Netherlands and Mexico (**Table 1** [32, 33]). Four guidelines were of very good quality, the remaining had minor shortcomings - mainly due to a limited reporting quality, including two which did not report on update procedures and therefore scored lowest in that domain (for details of the quality appraisal see **Web-Supplement 3~~4~~**).

In total, we extracted 246 recommendations (median: 27 recommendations per guideline (IQR: 13 to 52, range: 7-57)). The most common recommendations addressed the need for a thorough assessment of interactions and individualized management of patients (n=69 recommendations each), followed by identifying patient's preferences and goal setting (n=50), monitoring and follow-up (n=32), and identification of the target population (n=26) (**Figure 2**). Some of the recommendations were not specific to a single domain, for example, recommendations on individualized management also incorporated elements of monitoring and follow up.

[About here: Figure 1: Results of the search and selection process (flow chart)]

[About here: Table 1: Characteristics of included guidelines]

[About here: Figure 2: Distribution of recommendations per topic and guideline]

Identification of the target population

In one guideline, a systematic search for existing risk predicting models revealed many models for patients with multimorbidity but not for patients with polypharmacy [28]. This guideline recommended the identification of adults with multimorbidity at risk of adverse events (e.g., unplanned hospital admission or admission to a care home) using prognostic models – either opportunistically during routine care or proactively using the electronic medical record (EMR) [28]. Five guidelines provided information about risk factors for negative health outcomes covering different dimensions, such as condition-, medication-, adherence-related, and risks related to social context and health care utilization [25, 26, 28-30]. Condition-related risk factors included the presence of certain chronic diseases such as depression, dementia or cognitive decline, combinations of chronic mental and physical diseases such as diabetes and schizophrenia, the presence of conditions or events such as frailty, falls, non-specific symptoms and a worsening of health [25, 28-30]. Medication-related risks referred to drugs with a narrow therapeutic range, high potential for drug-drug interactions, the need for constant monitoring, psychotropic drugs and where patients received a suboptimal benefit from pharmaceutical treatment [26, 29]. Patients with non-adherence, difficulties managing their treatment regimen due to a high treatment burden or administration problems were also regarded as being at risk [25, 28, 29]. Social risk

factors included problems managing day-to-day activities, not living independently, limited ability to understand treatment recommendations (e.g., language problems and health literacy), advanced age and limited access to health care [25, 28-30]. The involvement of multiple and uncoordinated health care professionals and low uptake of care plans was noted to increase unplanned hospital admissions and emergency care [25, 28, 29].

Interaction assessment

According to the Ariadne Principles the interaction assessment should be conducted as a thorough assessment of diseases (including severity and impact on quality of life and functioning) and treatments (including potential interactions, adverse drug reactions, under-use and adherence), and of the clinical status and psychosocial context of the patient [15]. Seven guidelines addressed this principle, covering the medical history, a clinical and psychosocial assessment, a medication review and consideration of previous health services utilization [25-31]. Regarding the medical history, the documentation of all known diagnoses and conditions as well as existing laboratory test results and medication-related problems in the electronic medical record was recommended [25, 29]. One guideline [25] recommended the use of a structured questionnaire [34] about medication use, problems, experiences, worries and expectations. The clinical assessment included identification of a wide range of health problems as well as an assessment of physiological status and frailty [27, 28]. Recommendations on a medication review were at the core of the included polypharmacy guidelines, but were also addressed in the multimorbidity guidelines. One of them stressed the importance of informational continuity, in order to explore encounters with other physicians or health care professionals and changes in management over time [29] (**Textbox 1**).

[About here:

Textbox 1: Key recommendations on interaction assessment

Guiding principles

- Assess diseases, health problems, clinical and functional status, pharmacological and non-pharmacological treatment including potential interactions between diseases and treatments as well as the burden for the patient and take into account his/her psychosocial context [25-31].

- Involve patients and their family members or carers, where appropriate, in the assessment process, and clarify and resolve misconceptions [26, 31].
- Explore patient's contacts with other health care professionals and any related changes in management and consider using information technology support and a multidisciplinary team-based approach [26, 28, 29, 31].

Specific recommendations on clinical management

- **Clinical assessment**: Assess the management of health problems such as chronic pain, depression and anxiety, the presence of incontinence, the physiological and functional status and whether there are nutritional and hydration requirements [27, 28].
- **Medication review:** Evaluate the risk-benefit of each drug, its possible interactions and adverse effects, adherence to treatment and unmet needs and be aware of possible prescribing cascades [29, 30]. Assess the use of prescriptions, over-the-counter and food supplements or medicinal herbs and the actual implementation of a medication plan [29, 30]. Undertake a medication review regularly once a year; more often if needed, for example in relation to hospital stays: on admission, transfers between wards and at discharge [27, 29]. Use multiple methods such as health record reviews, patient surveys during consultations in practice or home visits and direct observation of medicines administration [26-29].

Specific recommendations on self-management support†

- Establish disease and treatment burden, its effect on day-to-day life including mental health, general wellbeing and quality of life [28]. Establish additional burden arising from caring responsibilities [27]. These features need to be incorporated when considering patients' capacity and the supports needed for self-management of long-term conditions and treatments [27].

Toolbox

Clinical assessment

- Instruments determining patient capacity and vulnerability to interactions, such as gait speed, self-reported health status, the PRISMA-7 questionnaire [35] (*primary care*), the 'Timed Up and Go' test [36], the Physical Activity Scale for the Elderly [37] (*hospital outpatients*) and Comprehensive Geriatric Assessment, CGA [38] (*hospitals*).

Medication assessment

- *Instruments based on implicit criteria*, such as MAI (Medication Appropriateness Index) [39], ACOVE (Assessing Care of Vulnerable Elders) [40], and the STRIP method (Systematic Tool to Reduce Inappropriate Prescribing) [28].

- *Instruments based on explicit criteria*, such as the STOPP (Screening Tool of Older Person's Prescriptions), START (Screening Tool to Alert doctors to Right Treatment) [41, 42], PIM lists (Potentially Inappropriate Medications, e.g., Beers criteria, EU-PIM list) [21, 43], FORTA (Fit for The Aged) [44-46], QT drug lists [47], databases on interactions, dosage adaption according to renal function and fall risk increasing drugs.

†We defined self-management support as the care and encouragement provided to people with chronic conditions and their families to help them understand their central role in managing their illness, make informed decision about care and engage in healthy behaviors (MacColl Center [50]).
End of Textbox 1]

Patient's preferences, prioritization and goal setting

All but one of the guidelines provided recommendations on eliciting patient preferences and expectations, including guidance on the level of involvement of patients and carers. The recommendations also focus on the process of shared decision making in relation to treatment options and the way they are communicated [24-29, 31]. Two guidelines provided specific recommendations regarding decision aids as tools to support shared decision-making [26, 28]. Additionally, one guideline referred to the need for specific skills and expertise in the use of patient decision aids [26] (**Textbox 2**).

[About here:

Textbox 2: Key recommendations on eliciting patient's preferences and sharing realistic treatment goals.

Guiding principles

- Patients should be encouraged to express their personal values, aims and priorities. The attitude of the patient regarding the treatment and its potential benefit has to be explored [26, 28, 31]. This includes addressing medical, psychological, emotional, social, personal, sexual, spiritual, cultural needs, vision, hearing and communication needs, environmental care needs and palliative and end of life care needs [24, 27].

Specific recommendations on clinical management

- Discuss with the person the purpose of the approach to care, for example, to improve quality of life and function. This might include reducing treatment burden and optimizing care and support by identifying possible improvements in medication and reducing inappropriate or medication with negative effect [28].
- The process of eliciting patient preferences requires several steps: 1) recognize when the patient with multimorbidity is facing a "preference sensitive" decision; 2) ensure patients with multimorbidity are adequately informed about the expected benefits and harms and 3) elicit patient preferences only after the individual with multimorbidity is sufficiently informed [24].
- Explore patient's expectations and objectives about treatments before prescribing [29].
- Find out what level of involvement in decision-making the person would like and avoid making assumptions about this [26].
- Use the best available evidence when making decisions with or for individuals, together with the clinical expertise and the person's values and preferences [26].

Specific recommendations on self-management support

- Encourage patients with multimorbidity to clarify what is important to them, including their personal goals, values and priorities [28].

Toolbox

- Use a patient decision aid to help them make a preference-sensitive decision that involves trade-offs between benefits and harms, if available in high quality and appropriate in the context of the consultation as a whole [26].

End of Textbox 2]

Individualized management

All guidelines provided recommendations on this topic. Guiding principles referred to the optimization of treatment benefits over possible harms in pharmaceutical and non-pharmaceutical interventions. They also referred to information that should be included in medication plans – and, in wider care plans, including social and tele-healthcare [24, 26-30]. Recommendations on treatment communication (with or without direct consideration of self-management support) was a strong focus in four guidelines [26-29] and the coordination of care was addressed in more than half of guidelines [24, 26-29, 31]. Self-management support was addressed indirectly in relation to individualized management in half of the

guidelines [26-29]. The guidelines which addressed this issue focused primarily on self-management support for medicines management and support with care coordination (**Textbox 3**).

[About here:

Textbox 3: Key recommendations on individualized management

Guiding principles

- Use strategies for choosing therapies that optimize benefit, minimize harm, and enhance quality of life for patients with multimorbidity and consider treatment burden, complexity and feasibility [24, 28].
- Consider the applicability and quality of evidence such as study population, study duration, benefits in terms of absolute risk reduction and time horizon. Studies in younger patients without multimorbidity and polypharmacy and with short follow-up times and relative risk reduction may overestimate benefits and underestimate harms, and time horizon to benefit may be too late to achieve relevant treatment effects in older patients with multimorbidity and polypharmacy [24, 28, 30].
- In deprescribing medication(s), follow a systematic approach including identification and prioritization of medicines to be discontinued, stopping one at a time and consideration of tapering dosage rather than stopping, and planning and communicating with patients (and caregivers, if necessary) [29].
- Ensure care plans are tailored to each person, giving them choice and control and recognizing the inter-related nature of multiple long-term conditions [27].
- Health professionals involved in the treatment of patients with multimorbidity should share relevant information about the person and their medicines – in particular when patients are transferred to another care setting [27, 31].

Specific recommendations on clinical management

- Be aware that the management of risk factors for future disease can be a major treatment burden for people with multimorbidity and should be carefully considered when optimizing care [28].
- When prescribing medications such as statins and bisphosphonates, be aware that they may only provide benefit to elderly patients who have estimated survival greater than five years [30].

- The selection of a primary pharmacy is recommended to support the coordination of self-administered drugs with regard to dosage instructions and overall medication regimens, particularly when there are multiple prescribers [29].
- Ensure there is community based multidisciplinary support for patients with multimorbidity with social care needs which might include, for example, a physiotherapist or occupational therapist, a mental health social worker or psychiatrist, and community based services [27].

Specific recommendations on self-management support

- Consider using an individualized patient-held medication plan that should include information on drugs and specific instruction for usage; if dosage is 'as needed', exact information about indication and individual dosage must be provided (single dose, interval and maximal daily dosage); in short-term prescriptions, the prospective end date should be specified and information about medication history and reduced renal function should be included when indicated [29].
- Develop care plans that address ongoing medical and social care needs for individual patients that focus on enhancing social connectedness and community involvement and also ensuring that carers' needs are taken into consideration and that these care plans do not add to treatment burden [26-28].
- Ensure ongoing and adequate communication, in particular around medicines and wider care plans with identification of perceived benefits and ensuring patient involvement in the process [26-28].
- Consider with the person whether there are tele-healthcare options that may support them to make informed choices to help them manage their conditions, as well as other potential benefits, risks and costs [27].
- Consider the use of named care coordinators who can agree a course of action with patients and their carers if these needs cannot be addressed by existing health and social care professionals. This may be particularly important at times of transition, for example when considering moving to a care home [27].

Toolbox

- Computerized decision support systems (CDSS) that support decision-making and prescribing but do not replace clinical judgment; and options for tele-healthcare [26, 27].

End of Textbox 3]

Monitoring and follow-up

In five guidelines, aspects of follow-up and monitoring of treatment effects as well as goal attainment were addressed [25-29]. Recommendations covered strategies in care planning, self-management and medication-related aspects, the communication with patients including patient information and safety instructions as well as adherence, the coordination of care regarding medication appropriateness and safety concerns, possible collaboration with pharmacies, the involvement of care coordinators, referrals and discharge management [25-29]. Additionally, organizational or health care professionals' responsibilities with regard to follow-up of medication-related aspects and the specific conditions in care homes were addressed in two guidelines [26, 27] (**Textbox 4**).

[About here:

Textbox 4: Key recommendations on monitoring and follow-up

Guiding principles

- Review and update medication / care plans regularly to recognize and record changes in needs [25-29].

Specific recommendations on clinical management

- Monitor treatment effects and clinical parameters, as well as side effects at follow-up appointments. Check for non-specific symptoms as potential indicators of complications resulting from treatment changes such as dry mouth, weakness / exhaustion / fatigue, drowsiness, reduced alertness, sleep disturbances, motor disorders, tremors, falls; constipation, diarrhea, incontinence, loss of appetite, nausea; skin rashes, itching; depression or lack of interest in usual activities, confusion (temporary or chronic), hallucinations, fear and agitation, vertigo, tinnitus and control clinical parameters (e.g., health examination, if necessary lab tests, ECG). Consider increasing the frequency of follow-up visits following treatment changes [29].
- Monitor treatment after discharge: due to the (usually) short duration of a hospital stay, newly introduced medications may not have reached steady state at discharge, because inpatient care is frequently shorter than 4 to 5 half-lives of prescribed drugs. Effectiveness and side effects cannot necessarily be properly assessed in hospital [29].
- Monitor ongoing treatment including demonstrations of medication administration (e.g., inhalers) and effective forms of self-monitoring [29].

- Consider continuing to offer information and support to people and their carers, even if they have declined this previously, recognizing that long−term conditions can be changeable or progressive, and people's information needs may change [26].

Specific recommendations on self-management support

- Review the self-management plan to ensure the person does not have problems using it [26].
- Health and social care providers should explain to patients, and their family members or carers where appropriate, how to identify and report medicines-related patient safety incidents that arise during follow-up periods [26].
- Self-management plans could include specific arrangements about follow-up to review the decisions made [28].

End of Textbox 4]

Discussion

Summary of included guidelines

Our review identified eight comprehensive guidelines addressing older patients with multimorbidity or polypharmacy. Many guidelines had to be excluded, mainly due to a lack of reporting of systematic search strategies. The vast majority of the included guidelines were of good quality according to the MiChe checklist [22, 23]. Interestingly, only three out of eight guidelines used levels of evidence and grades of recommendations, despite the recognition of their importance [48]. This may reflect the fact that evidence for effective interventions in this population is scarce and that expert consensus may often represent the best available evidence. However, this has also been the case for disease-specific guidelines. For example in chronic heart failure, a review found that about half of the guideline recommendations were consensus based [18]. There is a clear need to prioritize research to generate evidence for effective interventions in 'real world-patients'.

The recommendations included in the guidelines covered a broad spectrum of aspects related to clinical management and self-management and included recommendations beyond traditional realms of clinical guidelines (e.g., regarding structural requirements of organizations, knowledge and skills of different care providers). The recommendations varied in their specificity – from abstract guiding principles to detailed specific recommendations on necessary changes in practice and which tools may provide

actionable support. Multimorbidity guidelines more often provided generic guiding principles whereas those addressing polypharmacy tended to provide more specific recommendations and tools, but both remarkably neglected cognitive dysfunction. This is surprising for a frequent problem in this population, and one that is frequently underdiagnosed and has a major impact on health status and significant implications for self-management and interference with the health care system [49]. Furthermore, recommendations about pharmacologic treatment outweighed other types of recommendations (e.g. physical exercise) and no guideline specifically provided decision support for screening or diagnostic procedures. The impact of multimorbidity on diagnosis is not trivial as it can affect diagnostic accuracy and cause diagnostic delay with important implications for prognosis [50, 51].

The elicitation and consideration of patient preferences were considered as an essential part of the management of patients with multimorbidity and polypharmacy by all included guidelines. Caution was recommended in the use of decision aids because they were mainly developed for single diseases. It is noteworthy, that only three guidelines involved patient representatives in the development process.

Barriers and facilitators to implementation of recommendations - models of care

A major barrier to implementation is that current health care models are based on the single disease paradigm, with the exceptions of certain settings (primary care) and specialties services (geriatrics, mental health) ~~(see review no. 3 [ref] in this issue)~~. Guideline recommendations generally did not account for settings, with the exception of differentiated recommendations on instruments that can assist a clinician in determining patient functional capacity. For example, the comprehensive geriatric assessment has been shown to be effective in hospitals [38] but not in primary care [52]. Geriatricians and family physicians, while sharing a holistic approach, typically operate under different frameworks. Geriatricians are more often based in hospitals and provide care for the 'geriatric patient', while family physicians provide longitudinal care for unselected patients [53-55]. This has important implications in primary care, for example, in the organization of long-term follow-up and monitoring but also in the identification of patients with multimorbidity and polypharmacy who are at risk of developing negative health outcomes – that is to differentiate between the 'fit and active' and people in need for an intensified care approach [28]. Research is needed that supports reliable methods for ensuring that those most at risk of adverse events are identified and benefit from appropriate interventions.

The complexities associated with the management of multimorbidity and polypharmacy make it advisable to ensure the involvement of other health and social care professionals for patients with low

health literacy or a complex social background. Multi-professional care teams including social workers – and in certain countries, care coordinators– may facilitate the implementation of recommendations if a context-specific tailoring of the recommendations is warranted.

Guidelines recommend clinicians to encourage self-management but the evidence for specific self-management support programs on multimorbidity is lacking [56]. Further research is needed on interventions that support priority setting and strategies to reduce barriers to self-management.

Communication with patients

All guidelines emphasized the importance of communication with patients and their carers about the patient's needs, priorities and preferences for improving patient-centered health outcomes and minimizing the burden of care and overtreatment. Decision aids to support this communication process have been developed generally for single chronic diseases. Decisions about health care for patients with multimorbidity require a more individualized approach that considers outcomes across conditions, such as overall health related quality of life, functioning or symptom-free survival.

Patient's preferences for prioritized outcomes may shift over time [57] but also with regard to the alternatives [58, 59]. Repeated communication about the importance and prioritization of outcomes is therefore imperative. Instruments to communicate about prioritization and preferences with regard to outcomes have been developed, again mostly with a condition specific approach [60-62] and limited psychometric properties [61]. Individual goal setting and prioritization are core tasks in individualizing the care for patients with multimorbidity. Although interventions have been developed to support this collaborative process between patients and clinicians, the evidence supporting their effectiveness is still lacking [56]. Which components of these often multi-faceted interventions are most relevant is not clear [63].

Guidelines on multimorbidity vs. polypharmacy

Existing guidelines follow concepts on multimorbidity (diagnosis based) or polypharmacy (treatment based) but the issues raised are relevant to essentially the same patient population in clinical practice. Medication reviews for example, were at the core of the polypharmacy and multimorbidity guidelines and the review itself must take into consideration both patient's conditions and treatments. The

separate production of guidelines addressing either multimorbidity or polypharmacy seems arbitrary and their combination would also relieve the burden – for developers and users.

Limitations

The systematic guideline review method offers a transparent and comprehensive approach to the analysis of existing guidelines, but our in-depth text analysis may not be free from subjectivity with regard to the themes selected and presented in this review.

Concluding remarks

Our review identified eight comprehensive guidelines of good quality addressing older patients with multimorbidity or polypharmacy. The guideline recommendations covered a broad spectrum of aspects of clinical and self-management, beyond the realms of traditional disease-oriented guidelines. The recommendations varied in their specificity – from abstract guiding principles to detailed recommendations on necessary changes in practice and tools providing actionable support. The limited availability of reliable risk prediction models, feasible interventions of proven effectiveness and decision aids, as well as limited consensus on appropriate outcomes of care highlight major research deficits. An integrated approach to both multimorbidity and polypharmacy should be considered in future guidelines.

Conflict of interest statement

The authors have nothing to disclose.

Authors' contributions:

Drs. CM, JMV and JWB designed the concept and the program for the workshop and agreed upon with all authors. Drs. CM and JWB had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. Drs. AIGG, CM, JWB, MSB and TSN extracted the data and assigned them to the Ariadne framework. Drs. AIGG, CM, JWB, SMS, MSB and TSN drafted the information synthesis. Drs. CM, JWB, SMS, MET, KJ and JMV led the workshop. Drs. CM, JWB, JMV,

SMS, AIGG, and MC drafted the first manuscript and all authors substantially contributed to the conception, acquisition, analysis and interpretation of data, revised the manuscript critically for important intellectual content, and finally approved it to be published.

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Figures, Tables and Web-Supplements

Figure 1: Results of the search and selection process (flow chart)

Figure 2: Distribution of recommendations per topic and guideline

Table 1: Characteristics of included guidelines

Legend: *Used in 2/8 recommendations; †King's Fund definitions: Appropriate polypharmacy - 'Prescribing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimized and where the medicines are prescribed according to best evidence'; Problematic polypharmacy - 'The prescribing of multiple [medicines] inappropriately, or where the intended benefit of the [medicines are] not realized'[33]; ‡Guiding principles for medicines optimization (the Royal Pharmaceutical Society): '(1) aim to understand the patient's experience, (2) evidence based choice of medicines, (3) ensure medicines use is as safe as possible, (4) make medicines optimization part of routine practice' [32]. Abbreviations: ADR – adverse drug reaction, GoR – grade of recommendation, LoE – level of evidence, MM – multimorbidity, PIM - potential inappropriate medication, PP – polypharmacy

Web-Supplement 1: search strategy and a complete list of web-sites visited

~~Web-Supplement 2: list of workshop participants~~

Web-Supplement 2~~3~~: list of excluded guidelines with reason for exclusion

Web-Supplement 3~~4~~: quality appraisal of included guidelines