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8	3	Evidence supporting the best clinical management of patients with multimorbidity and
9 10	4	polypharmacy: a systematic guideline review and expert consensus.
11 12 13	5	Running headline:
14 15	6	Clinical management of multimorbidity and polypharmacy.
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 Abstract:

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31 The complexity and heterogeneity of patients with multimorbidity and polypharmacy renders traditional 32 disease-oriented guidelines often inadequate and complicates clinical decision making. To address this 33 challenge, guidelines have been developed on multimorbidity or polypharmacy. To systematically 34 analyze their recommendations, we conducted a systematic guideline review using the Ariadne 35 principles for managing multimorbidity as analytical framework. The information synthesis included a 36 multi-step consensus process involving 18 multi-disciplinary experts from seven countries. We included 37 eight guidelines (four each on multimorbidity and polypharmacy) and extracted about 250 38 recommendations. The guideline addressed (1) the identification of the target population (risk factors); 39 (2) the assessment of interacting conditions and treatments: medical history, clinical and psychosocial 40 assessment including physiological status and frailty, reviews of medication and encounters with 41 healthcare providers highlighting informational continuity; (3) the need to incorporate patient 42 preferences and goal setting: eliciting preferences and expectations, the process of shared decision 43 making in relation to treatment options and the level of involvement of patients and carers; (4) 44 individualized management: guiding principles on optimization of treatment benefits over possible 45 harms, treatment communication and the information content of medication/care plans; (5) monitoring 46 and follow-up: strategies in care planning, self-management and medication-related aspects, 47 communication with patients including safety instructions and adherence, coordination of care regarding 48 referral and discharge management, medication appropriateness and safety concerns. The spectrum of 49 clinical and self-management issues varied from guiding principles to specific recommendations and 50 tools providing actionable support. The limited availability of reliable risk prediction models, feasible 51 interventions of proven effectiveness and decision aids, and limited consensus on appropriate outcomes 52 of care highlight major research deficits. An integrated approach to both multimorbidity and

- 53 polypharmacy should be considered in future guidelines.
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4	55	<b>Key words</b> : Multimorbidity [MeSH], Polypharmacy [MeSH], Patient-Centered Care [MeSH], Practice
5 6	56	Guideline [MeSH], Continuity of Patient Care [MeSH], older adults
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Page 5 of 73

**Background:** 

the outcomes less certain [3].

Family physicians care for patients with multiple conditions, known as multimorbidity [1], in up to 80% of

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

Patients with multiple conditions commonly take multiple prescriptions (polypharmacy) [4], which

treatments medication choice is less straightforward. Secondly, by increasing the possibility that

further increase complexity. Firstly, by increasing the potential for interactions between diseases and

additional medications will be prescribed to counteract side effects prescribing cascades may occur.

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

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# 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 diseaseoriented 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 

Page 7 of 73

#### Journal of Internal Medicine

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). 

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#### 132 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".

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#### 36 140 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
- 57 152 recommendation (GoR) as provided in the guideline. When recommendations addressed more than one

3 4	153	domain of the framework, we (CM, JWB) agreed upon the domain that best matched the	
5	154	recommendation to avoid duplicates.	
6 7 8	155		
9 10 11	156	Analysis	
12	157	The numbers of recommendations per topic and per guideline were described. We (AIGG, CM, JWB,	
13 14	158	SMS, TSN) conducted a thematic analysis, assigned categories and aggregated the recommendations as	
15 16	159	outlined above using the Ariadne framework.	
17 18	160		
19 20 21	161	Expert consensus process	
22 23	162	We discussed the results of the thematic synthesis at a two-day meeting in May 2018. This meeting	
24	163	included a symposium, in which the background to the topic was elucidated and a workshop with 18	
25 26	164	invited multidisciplinary experts – some of them with more than one area of expertise: geriatrics (7),	
27 28	165	primary care (6), public health and health services research (5), epidemiology (4) and	
29	166	pharmacy/pharmacology (2) from seven countries (Sweden (5), UK (4), USA (3), Italy and the Netherland	ls
30 31	167	(2), Germany and Ireland (1)). The group discussion was audio-recorded and transcribed and served as	
32	168	triangulation of the thematic analysis. The results of the guideline review and the group discussion were	ž
33 34 35	169	agreed upon and synthetized by all authors.	
36 37	170		
38 39	171		
40 41 42	172	Results:	
43 44	173	In total, we included eight guidelines, four on multimorbidity and four on polypharmacy [24-31] (Figure	
45	174	1; the list of excluded guidelines with reasons for exclusion is provided in Web-Supplement 2). Three	
40 47	175	guidelines were developed in the UK, two in Germany and one each in the US, the Netherlands and	
48 49	176	Mexico (Table 1 [32, 33]). Four guidelines were of very good quality, the remaining had minor	
50	177	shortcomings - mainly due to a limited reporting quality, including two which did not report on update	
52	178	procedures and therefore scored lowest in that domain (for details of the quality appraisal see Web-	
53 54 55 56 57 58	179	Supplement 3).	8

Page 9 of 73

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3	180	In total, we extracted 246 recommendations (median: 27 recommendations per guideline (IQR: 13 to 52,
4 5	181	range: 7-57)). The most common recommendations addressed the need for a thorough assessment of
6 7	182	interactions and individualized management of patients (n=69 recommendations each), followed by
8	183	identifying patient's preferences and goal setting (n=50), monitoring and follow-up (n=32), and
9 10	184	identification of the target population (n=26) (Figure 2). Some of the recommendations were not specific
11 12	185	to a single domain, for example, recommendations on individualized management also incorporated
13 14	186	elements of monitoring and follow up.
14 15 16	187	
17 19	100	[About boro: Figure 1: Pocults of the sourch and selection process (flow chart)]
19	100	[About here. Figure 1. Results of the search and selection process (now chart)]
20 21	189	
22 23	190	[About here: Table 1: Characteristics of included guidelines]
24	191	
25 26	192	[About here: Figure 2: Distribution of recommendations per topic and guideline]
27 28	102	
29	193	
30 31 32 33	194	Identification of the target population
	195	In one guideline, a systematic search for existing risk predicting models revealed many models for
34 35	196	patients with multimorbidity but not for patients with polypharmacy [28]. This guideline recommended
36 37 38	197	the identification of adults with multimorbidity at risk of adverse events (e.g., unplanned hospital
	198	admission or admission to a care home) using prognostic models – either opportunistically during
39 40	199	routine care or proactively using the electronic medical record (EMR) [28]. Five guidelines provided
41 42	200	information about risk factors for negative health outcomes covering different dimensions, such as
43	201	condition-, medication-, adherence-related, and risks related to social context and health care utilization
44 45	202	[25, 26, 28-30]. Condition-related risk factors included the presence of certain chronic diseases such as
46 47	203	depression, dementia or cognitive decline, combinations of chronic mental and physical diseases such as
48 40	204	diabetes and schizophrenia, the presence of conditions or events such as frailty, falls, non-specific
49 50	205	symptoms and a worsening of health [25, 28-30]. Medication-related risks referred to drugs with a
51 52	206	narrow therapeutic range, high potential for drug-drug interactions, the need for constant monitoring,
53 54 55	207	psychotropic drugs and where patients received a suboptimal benefit from pharmaceutical treatment
	208	[26, 29]. Patients with non-adherence, difficulties managing their treatment regimen due to a high
56 57	209	treatment burden or administration problems were also regarded as being at risk [25, 28, 29]. Social risk
58 59		9

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].

#### 216 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). 

43 232

45 233 [About here: 

47 234 **Textbox 1**: Key recommendations on interaction assessment

235 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].

Page 11 of 73

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3	239	٠	Involve patients and their family members or carers, where appropriate, in the assessment process,
4 5	240		and clarify and resolve misconceptions [26, 31].
6 7	241	•	Explore patient's contacts with other health care professionals and any related changes in
8	242		management and consider using information technology support and a multidisciplinary team-based
9 10	243		approach [26, 28, 29, 31].
11 12	244	Sp	ecific recommendations on clinical management
13 14	245	•	Clinical assessment: Assess the management of health problems such as chronic pain, depression
15	246		and anxiety, the presence of incontinence, the physiological and functional status and whether there
16 17	247		are nutritional and hydration requirements [27, 28].
18 19	248	•	Medication review: Evaluate the risk-benefit of each drug, its possible interactions and adverse
20	249		effects, adherence to treatment and unmet needs and be aware of possible prescribing cascades [29,
21	250		30]. Assess the use of prescriptions, over-the-counter and food supplements or medicinal herbs and
23 24	251		the actual implementation of a medication plan [29, 30]. Undertake a medication review regularly
25 26	252		once a year; more often if needed, for example in relation to hospital stays: on admission, transfers
20 27	253		between wards and at discharge [27, 29]. Use multiple methods such as health record reviews,
28 29	254		patient surveys during consultations in practice or home visits and direct observation of medicines
30 31	255		administration [26-29].
32	256	Sp	ecific recommendations on self-management support†
33 34	257	•	Establish disease and treatment burden, its effect on day-to-day life including mental health, general
35 36	258		wellbeing and quality of life [28]. Establish additional burden arising from caring responsibilities [27].
37	259		These features need to be incorporated when considering patients' capacity and the supports
38 39	260		needed for self-management of long-term conditions and treatments [27].
40 41	261	То	olbox
42 43	262	Cli	nical assessment
43 44	263	٠	Instruments determining patient capacity and vulnerability to interactions, such as gait speed, self-
45 46	264		reported health status, the PRISMA-7 questionnaire [35] ( <i>primary care</i> ), the 'Timed Up and Go' test
47 48	265		[36], the Physical Activity Scale for the Elderly [37] (hospital outpatients) and Comprehensive
49	266		Geriatric Assessment, CGA [38] (hospitals).
50 51	267	M	edication assessment
52 53	268	•	Instruments based on implicit criteria, such as MAI (Medication Appropriateness Index) [39], ACOVE
54	269		(Assessing Care of Vulnerable Elders) [40], and the STRIP method (Systematic Tool to Reduce
55 56	270		Inappropriate Prescribing) [28].
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3	271	• Instruments based on explicit criteria, such as the STOPP (Screening Tool of Older Person's
4 5	272	Prescriptions), START (Screening Tool to Alert doctors to Right Treatment) [41, 42], PIM lists
6 7	273	(Potentially Inappropriate Medications, e.g., Beers criteria, EU-PIM list) [21, 43], FORTA (Fit for The
8	274	Aged) [44-46], QT drug lists [47], databases on interactions, dosage adaption according to renal
9 10	275	function and fall risk increasing drugs.
11 12	276	
12 13	277	tWe defined self-management support as the care and encouragement provided to people with chronic
14 15	278	conditions and their families to help them understand their central role in managing their illness, make
16	270	informed decision about care and engage in healthy behaviors (MacColl Center [50])
17 18	279	Find of Texther 1
19	280	End of Textbox 1
20 21	281	
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23 24	282	Patient's preferences, prioritization and goal setting
25 26	283	All but one of the guidelines provided recommendations on eliciting patient preferences and
27	284	expectations, including guidance on the level of involvement of patients and carers. The
28 29	285	recommendations also focus on the process of shared decision making in relation to treatment options
30	286	and the way they are communicated [24-29, 31]. Two guidelines provided specific recommendations
31 32	287	regarding decision aids as tools to support shared decision-making [26, 28]. Additionally, one guideline
33 34	288	referred to the need for specific skills and expertise in the use of patient decision aids [26] (Textbox 2).
34 35	200	
36 37	289	
38	290	[About here:
39 40 41	291	<b>Textbox 2</b> : Key recommendations on eliciting patient's preferences and sharing realistic treatment goals.
42	292	Guiding principles
43 44		
45	293	<ul> <li>Patients should be encouraged to express their personal values, aims and priorities. The attitude of</li> </ul>
46 47	294	the patient regarding the treatment and its potential benefit has to be explored [26, 28, 31]. This
48 40	295	includes addressing medical, psychological, emotional, social, personal, sexual, spiritual, cultural
49 50	296	needs, vision, hearing and communication needs, environmental care needs and palliative and end
51 52	297	of life care needs [24, 27].
53 54	298	Specific recommendations on clinical management
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Page 13 of 73

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3 4 5 6 7	299	• Discuss with the person the purpose of the approach to care, for example, to improve quality of life
	300	and function. This might include reducing treatment burden and optimizing care and support by
	301	identifying possible improvements in medication and reducing inappropriate or medication with
8 9	302	negative effect [28].
9 10 11 12 13 14 15 16 17	303	• The process of eliciting patient preferences requires several steps: 1) recognize when the patient
	304	with multimorbidity is facing a "preference sensitive" decision; 2) ensure patients with
	305	multimorbidity are adequately informed about the expected benefits and harms and 3) elicit patient
	306	preferences only after the individual with multimorbidity is sufficiently informed [24].
	307	• Explore patient's expectations and objectives about treatments before prescribing [29].
18 19	308	Find out what level of involvement in decision-making the person would like and avoid making
19         20         21         22         23         24         25         26         27         28         29         30         31         32         33         34         35	309	assumptions about this [26].
	310	Use the best available evidence when making decisions with or for individuals, together with the
	311	clinical expertise and the person's values and preferences [26].
	312	Specific recommendations on self-management support
	313	• Encourage patients with multimorbidity to clarify what is important to them, including their personal
	314	goals, values and priorities [28].
	315	Toolbox
	316	• Use a patient decision aid to help them make a preference-sensitive decision that involves trade-offs
36 37	317	between benefits and harms, if available in high quality and appropriate in the context of the
38 39 40 41 42 43 44 45 46 47	318	consultation as a whole [26].
	319	End of Textbox 2]
	320	
	321	Individualized management
	322	All guidelines provided recommendations on this topic. Guiding principles referred to the optimization of
48	323	treatment benefits over possible harms in pharmaceutical and non-pharmaceutical interventions. They
49 50	324	also referred to information that should be included in medication plans – and, in wider care plans,
51 52	325	including social and tele-healthcare [24, 26-30]. Recommendations on treatment communication (with
53	326	or without direct consideration of self-management support) was a strong focus in four guidelines [26-
54 55	327	29] and the coordination of care was addressed in more than half of guidelines [24, 26-29, 31]. Self-
56 57	328	management support was addressed indirectly in relation to individualized management in half of the
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3	329	uidelines [26-29]. The guidelines which addressed this issue focused primarily on self-management	
4 5 6 7 8	330	upport for medicines management and support with care coordination ( <b>Textbox 3</b> ).	
	331		
9 10	332	About here:	
10	333	extbox 3: Key recommendations on individualized management	
12 13	334	Guiding principles	
14 15	335	Use strategies for choosing therapies that optimize benefit, minimize harm, and enhance quality o	f
16	336	life for patients with multimorbidity and consider treatment burden, complexity and feasibility [24	,
12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27	337	28].	
19 20	338	Consider the applicability and quality of evidence such as study population, study duration, benefit	S
20	339	in terms of absolute risk reduction and time horizon. Studies in younger patients without	
22 23	340	multimorbidity and polypharmacy and with short follow-up times and relative risk reduction may	
24 25	341	overestimate benefits and underestimate harms, and time horizon to benefit may be too late to	
25 26	342	achieve relevant treatment effects in older patients with multimorbidity and polypharmacy [24, 28	5.
27 28	343	30].	,
29	344	In deprescribing medication(s) follow a systematic approach including identification and	
30 31	345	prioritization of medicines to be discontinued, stopping one at a time and consideration of taperin	σ
32 33	346	dosage rather than stopping and planning and communicating with patients (and caregivers, if	5
34	2/17		
35 36 37 38	247	The cessary (29).	
	348	Ensure care plans are tailored to each person, giving them choice and control and recognizing the	
39	349	Inter-related nature of multiple long-term conditions [27].	
40 41	350	<ul> <li>Health professionals involved in the treatment of patients with multimorbidity should share releva</li> </ul>	nt
42	351	information about the person and their medicines – in particular when patients are transferred to	
43 44	352	another care setting [27, 31].	
45 46	353	pecific recommendations on clinical management	
47 48	354	Be aware that the management of risk factors for future disease can be a major treatment burden	
49	355	for people with multimorbidity and should be carefully considered when optimizing care [28].	
50 51	356	When prescribing medications such as statins and bisphosphonates, be aware that they may only	
52 53	357	provide benefit to elderly patients who have estimated survival greater than five years [30].	
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Page 15 of 73

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3	358	•	The selection of a primary pharmacy is recommended to support the coordination of self-
4 5	359		administered drugs with regard to dosage instructions and overall medication regimens, particularly
6 7	360		when there are multiple prescribers [29].
8 0	361	•	Ensure there is community based multidisciplinary support for patients with multimorbidity with
10	362		social care needs which might include, for example, a physiotherapist or occupational therapist, a
11 12	363		mental health social worker or psychiatrist, and community based services [27].
13 14	364	Sp	ecific recommendations on self-management support
15 16	365	•	Consider using an individualized patient-held medication plan that should include information on
17 18	366		drugs and specific instruction for usage; if dosage is 'as needed', exact information about indication
19	367		and individual dosage must be provided (single dose, interval and maximal daily dosage); in short-
20 21	368		term prescriptions, the prospective end date should be specified and information about medication
22 23	369		history and reduced renal function should be included when indicated [29].
24	370	•	Develop care plans that address ongoing medical and social care needs for individual patients that
25 26	371		focus on enhancing social connectedness and community involvement and also ensuring that carers'
27 28	372		needs are taken into consideration and that these care plans do not add to treatment burden [26-
29	373		28].
30 31	374	•	Ensure ongoing and adequate communication, in particular around medicines and wider care plans
32 33	375		with identification of perceived benefits and ensuring patient involvement in the process [26-28].
34 35	376	•	Consider with the person whether there are tele-healthcare options that may support them to make
36	377		informed choices to help them manage their conditions, as well as other potential benefits, risks and
37 38	378		costs [27].
39 40	379	•	Consider the use of named care coordinators who can agree a course of action with patients and
41	380		their carers if these needs cannot be addressed by existing health and social care professionals. This
42 43	381		may be particularly important at times of transition, for example when considering moving to a care
44 45	382		home [27].
46 47	383	То	olbox
48 49	384	•	Computerized decision support systems (CDSS) that support decision-making and prescribing but do
50	385		not replace clinical judgment; and options for tele-healthcare [26, 27].
51 52	225	-	
53 54	386	En	d of Textbox 3]
55 56	387		
57	388	M	onitoring and follow-up
58 59			15
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1 2		
3 1	389	In five guidelines, aspects of follow-up and monitoring of treatment effects as well as goal attainment
5	390	were addressed [25-29]. Recommendations covered strategies in care planning, self-management and
6 7	391	medication-related aspects, the communication with patients including patient information and safety
8 9	392	instructions as well as adherence, the coordination of care regarding medication appropriateness and
10	393	safety concerns, possible collaboration with pharmacies, the involvement of care coordinators, referrals
11 12	394	and discharge management [25-29]. Additionally, organizational or health care professionals'
13 14	395	responsibilities with regard to follow-up of medication-related aspects and the specific conditions in care
15 16	396	homes were addressed in two guidelines [26, 27] ( <b>Textbox 4</b> ).
17 18	397	
19 20	398	[About here:
21 22	399	Textbox 4: Key recommendations on monitoring and follow-up
23	400	Guiding principles
24 25	401	• Review and update medication / care plans regularly to recognize and record changes in needs [25-
26 27	402	29].
28 29 30	403	Specific recommendations on clinical management
31	404	• Monitor treatment effects and clinical parameters, as well as side effects at follow-up appointments.
32 33	405	Check for non-specific symptoms as potential indicators of complications resulting from treatment
34 35	406	changes such as dry mouth, weakness / exhaustion / fatigue, drowsiness, reduced alertness, sleep
36	407	disturbances, motor disorders, tremors, falls; constipation, diarrhea, incontinence, loss of appetite,
37 38	408	nausea; skin rashes, itching; depression or lack of interest in usual activities, confusion (temporary or
39 40	409	chronic), hallucinations, fear and agitation, vertigo, tinnitus and control clinical parameters (e.g.,
41 42	410	health examination, if necessary lab tests, ECG). Consider increasing the frequency of follow-up visits
42 43	411	following treatment changes [29].
44 45	412	• Monitor treatment after discharge: due to the (usually) short duration of a hospital stay, newly
46 47	413	introduced medications may not have reached steady state at discharge, because inpatient care is
48	414	frequently shorter than 4 to 5 half-lives of prescribed drugs. Effectiveness and side effects cannot
49 50	415	necessarily be properly assessed in hospital [29].
51 52	416	• Monitor ongoing treatment including demonstrations of medication administration (e.g., inhalers)
53	417	and effective forms of self-monitoring [29].
54 55		
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1 2							
3	418	•	Consider continuing to offer information and support to people and their carers, even if they have				
5	419		declined this previously, recognizing that long-term conditions can be changeable or progressive,				
6 7	420		and people's information needs may change [26].				
8 9 10	421		Specific recommendations on self-management support				
11 12	422	•	Review the self-management plan to ensure the person does not have problems using it [26].				
13	423	•	Health and social care providers should explain to patients, and their family members or carers				
14 15	424		where appropriate, how to identify and report medicines-related patient safety incidents that arise				
16 17	425		during follow-up periods [26].				
18	426	•	Self-management plans could include specific arrangements about follow-up to review the decisions				
19 20 21	427		made [28].				
22 23	428	End	d of Textbox 4]				
24	429						
25 26	430						
27 28	431	Discussion					
29 30 31	432	nmary of included guidelines					
32	433	Our	r review identified eight comprehensive guidelines addressing older patients with multimorbidity or				
33 34	434	poly	ypharmacy. Many guidelines had to be excluded, mainly due to a lack of reporting of systematic				
35 36	435	sea	rch strategies. The vast majority of the included guidelines were of good quality according to the				
37	436	MiC	Che checklist [22, 23]. Interestingly, only three out of eight guidelines used levels of evidence and				
38 39	437	gra	des of recommendations, despite the recognition of their importance [48]. This may reflect the fact				
40 41	438	tha	t evidence for effective interventions in this population is scarce and that expert consensus may often				
42	439	rep	resent the best available evidence. However, this has also been the case for disease-specific				
43 44	440	guio	delines. For example in chronic heart failure, a review found that about half of the guideline				
45 46	441	rec	ommendations were consensus based [18]. There is a clear need to prioritize research to generate				
47 48	442	evio	dence for effective interventions in 'real world-patients'.				
49 50	443	The	e recommendations included in the guidelines covered a broad spectrum of aspects related to clinical				
51 52	444	mai	nagement and self-management and included recommendations beyond traditional realms of clinical				
53	445	guio	delines (e.g., regarding structural requirements of organizations, knowledge and skills of different				
54 55	446	care	e providers). The recommendations varied in their specificity – from abstract guiding principles to				
56 57	447	det	ailed specific recommendations on necessary changes in practice and which tools may provide				
57 58 59 60			17				

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.

#### 462 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. 

477 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

Page 19 of 73

1 2			
3	479	health literacy or a complex social background. Multi-professional care teams including social workers	_
4 5	480	and in certain countries, care coordinators- may facilitate the implementation of recommendations if	а
6 7	481	context-specific tailoring of the recommendations is warranted.	
8 9	482	Guidelines recommend clinicians to encourage self-management but the evidence for specific self-	
10 11	483	management support programs on multimorbidity is lacking [56]. Further research is needed on	
12 13	484	interventions that support priority setting and strategies to reduce barriers to self-management.	
14 15 16	485		
10 17 18	486	Communication with patients	
19 20	487	All guidelines emphasized the importance of communication with patients and their carers about the	
20	488	patient's needs, priorities and preferences for improving patient-centered health outcomes and	
22 23	489	minimizing the burden of care and overtreatment. Decision aids to support this communication proce	SS
24	490	have been developed generally for single chronic diseases. Decisions about health care for patients wi	th
25 26	491	multimorbidity require a more individualized approach that considers outcomes across conditions, suc	ch
27 28	492	as overall health related quality of life, functioning or symptom-free survival.	
30	493	Patient's preferences for prioritized outcomes may shift over time [57] but also with regard to the	
31 32	494	alternatives [58, 59]. Repeated communication about the importance and prioritization of outcomes is	5
33 24	495	therefore imperative. Instruments to communicate about prioritization and preferences with regard to	С
34 35	496	outcomes have been developed, again mostly with a condition specific approach [60-62] and limited	
36 37	497	psychometric properties [61]. Individual goal setting and prioritization are core tasks in individualizing	
38	498	the care for patients with multimorbidity. Although interventions have been developed to support this	5
39 40	499	collaborative process between patients and clinicians, the evidence supporting their effectiveness is si	ill
41 42	500	lacking [56]. Which components of these often multi-faceted interventions are most relevant is not cle	ear
43	501	[63].	
44 45			
46 47	502		
47 48 49	503	Guidelines on multimorbidity vs. polypharmacy	
50 51	504	Existing guidelines follow concepts on multimorbidity (diagnosis based) or polypharmacy (treatment	
52	505	based) but the issues raised are relevant to essentially the same patient population in clinical practice.	
53 54	506	Medication reviews for example, were at the core of the polypharmacy and multimorbidity guidelines	
55 56	507	and the review itself must take into consideration both patient's conditions and treatments. The	
57			
58 59 60			19

508	separate production of guidelines addressing either multimorbidity or polypharmacy seems arbitrary and
500	their combination would also relieve the burden – for developers and users
203	their combination would also relieve the burden – for developers and users.
510	
511	Limitations
512	The systematic guideline review method offers a transparent and comprehensive approach to the
513	analysis of existing guidelines, but our in-depth text analysis may not be free from subjectivity with
514	regard to the themes selected and presented in this review.
515	
515	
516	Concluding remarks
517	Our review identified eight comprehensive guidelines of good quality addressing older patients with
518	multimorbidity or polypharmacy. The guideline recommendations covered a broad spectrum of aspects
519	of clinical and self-management, beyond the realms of traditional disease-oriented guidelines. The
520	recommendations varied in their specificity – from abstract guiding principles to detailed
521	recommendations on necessary changes in practice and tools providing actionable support. The limited
522	availability of reliable risk prediction models, feasible interventions of proven effectiveness and decision
523	aids, as well as limited consensus on appropriate outcomes of care highlight major research deficits. An
524	integrated approach to both multimorbidity and polypharmacy should be considered in future
525	guidelines.
526	
527	Conflict of interest statement
528	The authors have nothing to disclose.
529	
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531	Drs. CM, JMV and JWB designed the concept and the program for the workshop and agreed upon with all
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533	integrity of the data and the accuracy of the data analysis. Drs. AIGG, CM, JWB, MSB and TSN extracted
534	the data and assigned them to the Ariadne framework. Drs. AIGG, CM, JWB, SMS, MSB and TSN drafted

- 535 the information synthesis. Drs. CM, JWB, SMS, MET, KJ and JMV led the workshop. Drs. CM, JWB, JMV,

2		
3 4	536	SMS, AIGG, and MC drafted the first manuscript and all authors substantially contributed to the
5	537	conception, acquisition, analysis and interpretation of data, revised the manuscript critically for
6 7 0	538	important intellectual content, and finally approved it to be published.
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Page 26 of 73

Journal of Internal Medicine

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4 5 6	691	1979;	263-92.					
7 8	692	59	Verma AA, Razak F, Detsky AS. Understanding choice: why physicians should learn prospect					
9 10	693	theory	y. JAMA 2014; <b>311:</b> 571-2.					
11 12	694	60	Dierckx K, Deveugele M, Roosen P, Devisch I. Implementation of shared decision making in					
13 14 15	695	physic	cal therapy: observed level of involvement and patient preference. <i>Phys Ther</i> 2013; <b>93:</b> 1321-30	).				
15 16 17	696	61	Fried TR, Tinetti ME, Iannone L, O'Leary JR, Towle V, Van Ness PH. Health outcome prioritizat	ion				
18	697	as a to	ool for decision making among older persons with multiple chronic conditions. Arch Intern Med					
19 20 21	698	2011;	<b>171:</b> 1854-6.					
22 23	699	62	Mangin D, Stephen G, Bismah V, Risdon C. Making patient values visible in healthcare: a					
24	700	syster	natic review of tools to assess patient treatment priorities and preferences in the context of					
24 25 26 27	701	multir	multimorbidity. <i>BMJ Open</i> 2016; <b>6:</b> e010903.					
28 29	702	63	Vermunt N, Harmsen M, Westert GP, Olde Rikkert MGM, Faber MJ. Collaborative goal setting	Ş				
30	703	with elderly patients with chronic disease or multimorbidity: a systematic review. BMC Geriatr 2017; 17:						
31 32	704	167.						
33 34 25	705							
34         35         36         37         38         39         40         41         42         43         44         45         46         47         48         49         50         51         52         53         54         55         56	706							
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3	707	Figures, Tables and Web-Supplements
4 5	708	
6 7	709	Figure 1: Results of the search and selection process (flow chart)
8 9 10	710	Figure 2: Distribution of recommendations per topic and guideline
10 11 12	711	
13 14	712	Table 1: Characteristics of included guidelines
15 16	713	Legend: *Used in 2/8 recommendations; <sup>+</sup> King's Fund definitions: Appropriate polypharmacy -
17	714	'Prescribing for an individual for complex conditions or for multiple conditions in circumstances where
18 19	715	medicines use has been optimized and where the medicines are prescribed according to best evidence';
20 21	716	Problematic polypharmacy - 'The prescribing of multiple [medicines] inappropriately, or where the
22	717	intended benefit of the [medicines are] not realized'[33]; <sup>‡</sup> Guiding principles for medicines optimization
23 24	718	(the Royal Pharmaceutical Society): '(1) aim to understand the patient's experience, (2) evidence based
25 26	719	choice of medicines, (3) ensure medicines use is as safe as possible, (4) make medicines optimization
27	720	part of routine practice' [32]. Abbreviations: ADR – adverse drug reaction, GoR – grade of
28 29	721	recommendation, LoE – level of evidence, MM – multimorbidity, PIM - potential inappropriate
30 31 32	722	medication, PP – polypharmacy
33 34	723	
35 36	724	
37 38	725	Web-Supplement 1: search strategy and a complete list of web-sites visited
39 40 41	726	Web-Supplement 2: list of excluded guidelines with reason for exclusion
42 43	727	Web-Supplement 3: quality appraisal of included guidelines
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**Table 1**: Characteristics of included guidelines

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

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

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

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

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



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
		8	6	
	2	4	•	
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8	27	4	10	7
4	3	2		1
2	8	22	10	8
	9	6	27	15
10	9	6	11	•
	1. Identification of the target population          2         8         4         2         10	1. Identification of the target population2. Interaction assessment21211827432899109	1. Identification of the target population2. Interaction assessment3. Patient's preferences, prioritization and goal setting000000011001100110000000000000000000	1. Identification of the target population2. Interaction assessment3. Patient's preferences, prioritization and goal setting4. Individualized management0000000000011000011000000000000000000100000100000

<sup>3</sup>**Legend:** polypharmacy guideline

multimorbidity guideline

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#### 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	2018-02-20
	http://onlinelibrary.wiley.com/cochranelibrary/search/	
HSTAT	Health Services/Technology Assessment Texts	2018-02-20
	https://www.ncbi.nlm.nih.gov/books/NBK16710/	
Medline	Medline	2018-02-20
	http://www.pubmed.com	
TRIP	Trip Database	2018-02-20
	www.tripdatabase.com	

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

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

#### Evidence supporting the best clinical management of patients with multimorbidity and

### polypharmacy: a systematic guideline review and expert consensus.

Abbreviation	Name, country and internet address	Date
BÄK	Bundesärztekammer	2018-03-29
	www.baek.de	
BCC	British Columbia Council	2018-03-29
	www.bcguidelines.ca	
BGS	British Society of Geriatrics (UK)	2018-02-12
	http://www.bgs.org.uk	
BMA	British Medical Association	2018-03-29
	www.bma.org	
CADTH	Canadian Agency for Drug and Technologies Assessment	2018-02-12
	(Canada)	
	http://www.cadth.ca	
CGS	Canadian Geriatric Society (Canada)	2018-02-12
	http://www.canadiangeriatrics.ca	
CDHSH	Commonwealth Department of Human Services and Health	2018-02-12
	Comité d'Evaluation et de Diffusion des Innevations	2019 02 12
CEDIT	Technologiques (France)	2018-02-12
	http://cedit.aphp.fr/category/hta-2/	
СМА	Canadian Medical Association	2018-03-29
	www.cma.ca	
CFP	Canadian Family Physician (Canada)	2018-02-12
	http://www.cfp.ca	
CTFPHC	Canadian Task Force on Preventive Health Care (Canada)	2018-02-12
	http://www.ctfphc.org/	
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und	2018-02-14
	Familienmedizin	
	www.degam.de	
Deprescribing	Deprescribing.org (Canada)	2018-02-13
	http://www.deprescribing.org	
DGIM	Deutsche Gesellschaft für Innere Medizin	2018-02-14
	www.dgim.de	
DGK	Deutsche Gesellschaft für Kardiologie	2018-02-22
	www.dgk.org	
DIMDI	Deutsches Institut für Dokumentation und Information	2018-02-14
	www.dimdi.de	
Duodecim	Leitlinienseite von The Finnish Medical Society Duodecim (Finland)	2018-02-13
	https://www.duodecim.fi/english/duodecim/the-finnish-medical-	
	society-duodecim/	
# Evidence supporting the best clinical management of patients with multimorbidity and

# polypharmacy: a systematic guideline review and expert consensus.

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

#### Evidence supporting the best clinical management of patients with multimorbidity and

#### polypharmacy: a systematic guideline review and expert consensus.

#### Supplement 1

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

#### polypharmacy: a systematic guideline review and expert consensus.

#### Supplement 1

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

guideline review and expert consensus.

# Supplement 2

# List of excluded guidelines with reason

No CPG or guidance (when document is not a guideline nor a guideline type document: no systematic search was reported and no explicit recommendations were provided)

- 1. Abidi S. A knowledge-modeling approach to integrate multiple clinical practice guidelines to provide evidence-based clinical decision support for managing comorbid conditions. J Med Syst 2017; 41(193).
- Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia. Determinantes asociados al cumplimiento de los procedimientos clínicos empleados en el manejo de los pacientes crónicos en atención primaria. Madrid: Ministerio de Economía y Competitividad; 2015 [cited 2018 May 2]. Available from: URL: http://gesdoc.isciii.es/gesdoccontroller?action=download&id=08/04/2016-ec423e89b9.
- 3. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society 2015; 63(11):2227–46.
- 4. American Geriatrics Society Choosing Wisely Workgroup. American Geriatrics Society Identifies Five Things That Healthcare Providers and Patients Should Question. Journal of the American Geriatrics Society 2013; 61(4):622–31.
- 5. Arzneimittelkommission der deutschen Ärzteschaft. Arzneiverordnung in der Praxis; 2017. Arzneiverordnung in der Praxis 4.
- 6. Austad B, Hetlevik I, Mjolstad BP, Helvik AS. Applying clinical guidelines in general practice: a qualitative study of potential complications. BMC Family Practice 2016; 17(92).
- 7. Banerjee S. Multimorbidity older adults need health care that count past one. The Lancet 2014; 385(9968):587–9.
- 8. Barbabella F, Melchiorre MG, Quattrini S, Papa R, Lamura G. How can eHeath improve care for people with multimorbidity in Europe. Health Systems and Policy Analysis 2017; Policy Brief 25.
- 9. Boult C, Green AF, Boult LB, Pacala JT, Snyder C, Leff B. Successful Models of Comprehensive Care for Older Adults with Chronic Conditions: Evidence for the Institute of Medicine's "Retooling for an Aging America" Report. Journal of the American Geriatrics Society 2009; 57(12):2328–37.
- 10. Cadogan CA, Ryan C, Hughes CM. Appropiate polypharmacy and medicine safety: when many is too many. Drug Saf 2016; 39:109–16.
- 11. Centers for Medicare & Medicaid Services. Chronic Conditions among medicare beneficiaries: a methodological overview; 2017 [cited 2018 May 3]. Available from: URL: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/Methods\_Overview.pdf.
- 12. Du Buffel Vaure C, Ravaud P, Baron G, Barnes C, Gilberg S, Boutron I. Potential workload in applying clinical practice guidelines for patients with chronic conditions and multimorbidity: a systematic analysis. BMJ Open 2016; 6(e010119).
- Guthrie B, Thompson A, Dumbreck S, Flynn A, Alderson P, Nairn M et al. Better guidelines for better care: accounting for multimorbidity in clinical guidelines – structured examination of exemplar guidelines and health economic modelling. Health Services and Delivery Research 2017; 5(16).
- 14. Hajat C, Stein E, Yach D. Multiple Chronic Conditions; 2017 [cited 2018 May 3]. Available from: URL: http://www.tevapharm.com/files/docs/Teva\_MCC\_Report.pdf.
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# Page 45 of 73

### Journal of Internal Medicine

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

consensus.

# Supplement 3

# Table 1: Quality appraisal of included guidelines

MiChe items Guidelines	1. Identificati on of key recommen dations and comprehen sibleness	2. Specificatio n of the guideline's target audiences and scope	3. Specificatio n of the objectives and the target population	4. Independe nce and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguit y of recommen dations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommen dation 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

2		
3 4	1	Article type: Review - JIM-18-0656-R21 (first-second revision)
5 6	2	Title:
7 8	3	Evidence supporting the best clinical management of patients with multimorbidity and
9 10 11	4	polypharmacy: a systematic guideline review and expert consensus.
11 12 13	5	Running headline:
14 15	6	Clinical management of multimorbidity and polypharmacy.
16 17 18	7	Authors:
19	8	Christiane Muth <sup>1*</sup> , Jeanet W. Blom <sup>2*</sup> , Susan M. Smith <sup>3</sup> , Kristina Johnell <sup>4</sup> , Ana Isabel Gonzalez-
20 21	9	Gonzalez <sup>1</sup> , Truc S. Nguyen <sup>1</sup> , Maria-Sophie Brueckle <sup>1</sup> , Matteo Cesari <sup>5</sup> , Mary E. Tinetti <sup>6</sup> , Jose M.
22 23	10	Valderas <sup>7</sup>
24 25 26	11	
20 27 28	12	Affiliation:
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31 32	14	<sup>2</sup> Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The
33 34	15	Netherlands
35 36	16	<sup>3</sup> HRB Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons in
37 38 39	17	Ireland (RCSI), Dublin, Ireland
40	18	<sup>4</sup> Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institute
41 42 43	19	and Stockholm University, Stockholm, Sweden
44 45	20	<sup>5</sup> Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Università di Milano, Milan, Italy
46 47	21	<sup>6</sup> Division of Geriatrics, Department of Internal Medicine, School of Medicine, Yale University, New
47 48 49	22	Haven, CT, USA
50	23	<sup>7</sup> Health Services and Policy Research Group, APEx Collaboration for Academic Primary Care, NIHR
51 52 53	24	PenCLAHRC, University of Exeter Medical School, Exeter, UK
54 55 56 57 58 59 60	25	* Joint first authors

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3 4 5 6 7 8	26 27 28 29	Address for correspondence: Dr. Christiane Muth, MPH, Institute of General Practice, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, eMail: <u>muth@allgemeinmedizin.uni-frankfurt.de</u> ; telephone: +49-69-6301-4149/-5687; fax: +49-69- 6301-6428
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#### 30 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.

1 2		
3	55	Key words: Multimorbidity [MeSH], Polypharmacy [MeSH], Patient-Centered Care [MeSH], Practice
4 5 6	56	Guideline [MeSH], Continuity of Patient Care [MeSH], older adults
7 8	57	
9 10	58	
11 12 12	59	WORD count including text boxes: about 5,800 (max: 7,000) $\rightarrow$ 1015% reduction $\rightarrow$ target word count
15 14 15	60	4,930 5,200 (now: 5,023 words)
16 17 18 19 20 21 22 23 24 25 26 27 28 9 30 12 33 45 36 37 89 40 41 23 44 56 27 28 9 30 31 23 34 56 37 89 40 41 24 34 56 57 56 57 58 90	61	

#### **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

1 2		
3	93	key concepts they address. To facilitate the interpretation and actionability of the findings, we used the
4 5	94	previously published Ariadne principles [15], which provide a framework to guide care delivery in
6 7	95	patients with multimorbidity. At the core, the sharing of realistic treatment goals by physicians and
8	96	patients results from i) an interaction assessment, i.e., the thorough assessment of diseases and
10	97	treatments including their potential interactions, the patient's clinical status, their context as well as a
11 12	98	consideration of treatment burden; ii) the prioritization of health problems taking into account the
13 14	99	patient's preferences – his or her most and least desired outcomes; and iii) an individualized
15	100	management plan which outlines the best options of care in diagnostics, treatment, and prevention to
16 17	101	achieve the goals; iv) goal attainment is followed-up with a re-assessment in planned visits and v) the
18 19	102	occurrence of new or changed conditions, such as an increase in severity, or a changed context may
20	103	trigger a re-evaluation of the previous steps[15].
21 22	104	
23 24	101	
25	105	
26 27	106	Methods:
28 29	407	We can deated a medified automatic cuidaling region [40] followed by a wedge on the second second
30	107	we conducted a modified systematic guideline review [18] followed by a workshop-based consensus
32	108	meeting with multidisciplinary experts from North America and Europe.
33 34	109	
35	110	Literature Search and Selection
30 37		
38 39	111	We conducted a systematic search for existing clinical practice guidelines in the electronic databases
40	112	MEDLINE, The Cochrane Library, Health Services/Technology Assessment Texts (HSTAT), 'Turning
41 42	113	Research Into Practice' (TRIP) and Guideline International Network (G-I-N) database, as well as in the
43 44	114	National Guideline Clearinghouse combining controlled terms and free text words, such as comorbidity,
45	115	multimorbidity, multiple conditions, polypharmacy, multiple drugs, multiple medications and older
46 47	116	adults. We conducted the searches in February and March 2018, dated back to the database inception.
48 49	117	In addition, we searched websites of guideline producing organizations including geriatric and primary
50 51	118	care societies (the complete list is provided in <b>Web-Supplement 1</b> ).
52	119	We included comprehensive guidelines or guideline-like documents on multimorbidity and
54	120	polypharmacy, if they were "systematically developed statements to assist practitioner and patient
55 56	121	decisions about appropriate health care for specific clinical circumstances" [19], if their purpose was "to
57 58 59 60		6

#### Journal of Internal Medicine

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).

19 131

#### 132 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".

34 139

#### 36 140 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
- 57 152 recommendation (GoR) as provided in the guideline. When recommendations addressed more than one

1 2		
3	153	domain of the framework, we (CM, JWB) agreed upon the domain that best matched the
4 5 6	154	recommendation to avoid duplicates.
7 8	155	
9 10 11	156	Analysis
12	157	The numbers of recommendations per topic and per guideline were described. We (AIGG, CM, JWB,
13 14	158	SMS, TSN) conducted a thematic analysis, assigned categories and aggregated the recommendations as
15 16	159	outlined above using the Ariadne framework.
17 18	160	
19 20 21	161	Expert consensus process
22 23	162	We discussed the results of the thematic synthesis at a two-day meeting in May 2018. This meeting
24	163	included a symposium, in which the background to the topic was elucidated and a workshop with 18
25 26	164	invited multidisciplinary experts – some of them with more than one area of expertise: geriatrics (7),
27 28	165	primary care (6), public health and health services research (5), epidemiology (4) and
29	166	pharmacy/pharmacology (2) from seven countries (Sweden (5), UK (4), USA (3), Italy and the Netherlands
30 31	167	(2), Germany and Ireland (1) <del>; see Web-Supplement 2</del> ). The group discussion was audio-recorded and
32 33	168	transcribed and served as triangulation of the thematic analysis. The results of the guideline review and
34	169	the group discussion were agreed upon and synthetized by all authors.
35 36 37	170	
38 39	171	
40 41 42	172	Results:
43 44	173	In total, we included eight guidelines, four on multimorbidity and four on polypharmacy [24-31] (Figure
45 46	174	1; the list of excluded guidelines with reasons for exclusion is provided in Web-Supplement 23). Three
40 47	175	guidelines were developed in the UK, two in Germany and one each in the US, the Netherlands and
48 49	176	Mexico (Table 1 [32, 33]). Four guidelines were of very good quality, the remaining had minor
50 51	177	shortcomings - mainly due to a limited reporting quality, including two which did not report on update
52	178	procedures and therefore scored lowest in that domain (for details of the quality appraisal see Web-
53 54 55	179	Supplement <u>3</u> 4).
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# Journal of Internal Medicine

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3 1	180	In total, we extracted 246 recommendations (median: 27 recommendations per guideline (IQR: 13 to 52,
5	181	range: 7-57)). The most common recommendations addressed the need for a thorough assessment of
6 7	182	interactions and individualized management of patients (n=69 recommendations each), followed by
8	183	identifying patient's preferences and goal setting (n=50), monitoring and follow-up (n=32), and
9 10	184	identification of the target population (n=26) (Figure 2). Some of the recommendations were not specific
11 12	185	to a single domain, for example, recommendations on individualized management also incorporated
13 14	186	elements of monitoring and follow up.
15 16 17	187	
18 19	188	[About here: Figure 1: Results of the search and selection process (flow chart)]
20 21 22	189	
23	190	[About here: Table 1: Characteristics of included guidelines]
24 25	191	
26 27	192	[About here: Figure 2: Distribution of recommendations per topic and guideline]
28 29	193	
30 31 32	194	Identification of the target population
33	195	In one guideline, a systematic search for existing risk predicting models revealed many models for
34 35	196	patients with multimorbidity but not for patients with polypharmacy [28]. This guideline recommended
36 37	197	the identification of adults with multimorbidity at risk of adverse events (e.g., unplanned hospital
38	198	admission or admission to a care home) using prognostic models – either opportunistically during
39 40	199	routine care or proactively using the electronic medical record (EMR) [28]. Five guidelines provided
41 42	200	information about risk factors for negative health outcomes covering different dimensions, such as
43	201	condition-, medication-, adherence-related, and risks related to social context and health care utilization
44 45	202	[25, 26, 28-30]. Condition-related risk factors included the presence of certain chronic diseases such as
46 47	203	depression, dementia or cognitive decline, combinations of chronic mental and physical diseases such as
48	204	diabetes and schizophrenia, the presence of conditions or events such as frailty, falls, non-specific
49 50	205	symptoms and a worsening of health [25, 28-30]. Medication-related risks referred to drugs with a
51 52	206	narrow therapeutic range, high potential for drug-drug interactions, the need for constant monitoring,
53	207	psychotropic drugs and where patients received a suboptimal benefit from pharmaceutical treatment
54 55	208	[26, 29]. Patients with non-adherence, difficulties managing their treatment regimen due to a high
56 57	209	treatment burden or administration problems were also regarded as being at risk [25, 28, 29]. Social risk
58 59		9

Page 55 of 73

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#### Journal of Internal Medicine

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44 45 46 47 48 49 50 51 52 53 54 55 56
44 45 46 47 48 49 50 51 52 53 54 55 56 57

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].

#### 216 Interaction assessment

217 According to the Ariadne Principles the interaction assessment should be conducted as a thorough 218 assessment of diseases (including severity and impact on quality of life and functioning) and treatments 219 (including potential interactions, adverse drug reactions, under-use and adherence), and of the clinical 220 status and psychosocial context of the patient [15]. Seven guidelines addressed this principle, covering 221 the medical history, a clinical and psychosocial assessment, a medication review and consideration of 222 previous health services utilization [25-31]. Regarding the medical history, the documentation of all 223 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 224 225 the use of a structured questionnaire [34] about medication use, problems, experiences, worries and 226 expectations. The clinical assessment included identification of a wide range of health problems as well 227 as an assessment of physiological status and frailty [27, 28]. Recommendations on a medication review 228 were at the core of the included polypharmacy guidelines, but were also addressed in the multimorbidity 229 guidelines. One of them stressed the importance of informational continuity, in order to explore 230 encounters with other physicians or health care professionals and changes in management over time 231 [29] (Textbox 1).

3 232

59 60

233 [About here:

234 **Textbox 1**: Key recommendations on interaction assessment

235 *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].

2			
3	239	•	Involve patients and their family members or carers, where appropriate, in the assessment process,
4 5	240		and clarify and resolve misconceptions [26, 31].
6 7	241	•	Explore patient's contacts with other health care professionals and any related changes in
8	242		management and consider using information technology support and a multidisciplinary team-based
9 10	243		approach [26, 28, 29, 31].
11 12	244	Sp	ecific recommendations on clinical management
13 14	245	•	Clinical assessment: Assess the management of health problems such as chronic pain, depression
15	246		and anxiety, the presence of incontinence, the physiological and functional status and whether there
16 17	247		are nutritional and hydration requirements [27, 28].
18 19	248	٠	Medication review: Evaluate the risk-benefit of each drug, its possible interactions and adverse
20	249		effects, adherence to treatment and unmet needs and be aware of possible prescribing cascades [29,
21 22	250		30]. Assess the use of prescriptions, over-the-counter and food supplements or medicinal herbs and
23 24	251		the actual implementation of a medication plan [29, 30]. Undertake a medication review regularly
25	252		once a year; more often if needed, for example in relation to hospital stays: on admission, transfers
26 27	253		between wards and at discharge [27, 29]. Use multiple methods such as health record reviews,
28 29	254		patient surveys during consultations in practice or home visits and direct observation of medicines
30 21	255		administration [26-29].
32	256	Sp	ecific recommendations on self-management support
33 34	257	٠	Establish disease and treatment burden, its effect on day-to-day life including mental health, general
35 36	258		wellbeing and quality of life [28]. Establish additional burden arising from caring responsibilities [27].
37	259		These features need to be incorporated when considering patients' capacity and the supports
38 39	260		needed for self-management of long-term conditions and treatments [27].
40 41	261	То	olbox
42	262	Cli	nical assessment
43 44	263	•	Instruments determining patient capacity and vulnerability to interactions, such as gait speed, self-
45 46	264		reported health status, the PRISMA-7 questionnaire [35] (primary care), the 'Timed Up and Go' test
47 48	265		[36], the Physical Activity Scale for the Elderly [37] (hospital outpatients) and Comprehensive
48 49	266		Geriatric Assessment, CGA [38] (hospitals).
50 51	267	Μ	edication assessment
52 53	268	•	Instruments based on implicit criteria, such as MAI (Medication Appropriateness Index) [39], ACOVE
54	269		(Assessing Care of Vulnerable Elders) [40], and the STRIP method (Systematic Tool to Reduce
55 56	270		Inappropriate Prescribing) [28].
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Page 57 of 73

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3 ⊿	271	Instruments based on explicit criteria, such as the STOPP (Screening Tool of Older Person's
5	272	Prescriptions), START (Screening Tool to Alert doctors to Right Treatment) [41, 42], PIM lists
6 7	273	(Potentially Inappropriate Medications, e.g., Beers criteria, EU-PIM list) [21, 43], FORTA (Fit for The
8	274	Aged) [44-46], QT drug lists [47], databases on interactions, dosage adaption according to renal
9 10	275	function and fall risk increasing drugs.
11 12	276	
13 14	277	<sup>+</sup> We defined self-management support as the care and encouragement provided to people with chronic
14	278	conditions and their families to help them understand their central role in managing their illness, make
16 17	279	informed decision about care and engage in healthy behaviors (MacColl Center [50]).
18 19	280	End of Textbox 1]
20 21	281	
22 23	202	Patient's proferences, prioritization and goal setting
24	202	
25 26	283	All but one of the guidelines provided recommendations on eliciting patient preferences and
27 20	284	expectations, including guidance on the level of involvement of patients and carers. The
28 29	285	recommendations also focus on the process of shared decision making in relation to treatment options
30 31 32	286	and the way they are communicated [24-29, 31]. Two guidelines provided specific recommendations
	287	regarding decision aids as tools to support shared decision-making [26, 28]. Additionally, one guideline
33 34 25	288	referred to the need for specific skills and expertise in the use of patient decision aids [26] ( <b>Textbox 2</b> ).
35 36	289	
37 38	290	[About here:
39 40 41	291	<b>Textbox 2</b> : Key recommendations on eliciting patient's preferences and sharing realistic treatment goals.
42 43	292	Guiding principles
44 45	293	• Patients should be encouraged to express their personal values, aims and priorities. The attitude of
46 47	294	the patient regarding the treatment and its potential benefit has to be explored [26, 28, 31]. This
48	295	includes addressing medical, psychological, emotional, social, personal, sexual, spiritual, cultural
49 50	296	needs, vision, hearing and communication needs, environmental care needs and palliative and end
51 52	297	of life care needs [24, 27].
53 54 55 56	298	Specific recommendations on clinical management
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3	299	• Discuss with the person the purpose of the approach to care, for example, to improve quality of life
5 6 7 8 9	300	and function. This might include reducing treatment burden and optimizing care and support by
	301	identifying possible improvements in medication and reducing inappropriate or medication with
	302	negative effect [28].
10	303	• The process of eliciting patient preferences requires several steps: 1) recognize when the patient
11 12	304	with multimorbidity is facing a "preference sensitive" decision; 2) ensure patients with
13 14	305	multimorbidity are adequately informed about the expected benefits and harms and 3) elicit patient
15	306	preferences only after the individual with multimorbidity is sufficiently informed [24].
16 17 18 19 20 21 22	307	• Explore patient's expectations and objectives about treatments before prescribing [29].
	308	Find out what level of involvement in decision-making the person would like and avoid making
	309	assumptions about this [26].
	310	• Use the best available evidence when making decisions with or for individuals, together with the
23 24	311	clinical expertise and the person's values and preferences [26].
25 26 27 28 29 30 31 32 33 34 35	312	Specific recommendations on self-management support
	313	• Encourage patients with multimorbidity to clarify what is important to them, including their personal
	314	goals, values and priorities [28].
	315	Toolbox
	316	• Use a patient decision aid to help them make a preference-sensitive decision that involves trade-offs
36 37	317	between benefits and harms, if available in high quality and appropriate in the context of the
38 39	318	consultation as a whole [26].
40 41	319	End of Textbox 2]
42 43	320	
44 45	321	Individualized management
46 47	322	All guidelines provided recommendations on this topic. Guiding principles referred to the optimization of
48 ⊿q	323	treatment benefits over possible harms in pharmaceutical and non-pharmaceutical interventions. They
50	324	also referred to information that should be included in medication plans – and, in wider care plans,
51 52	325	including social and tele-healthcare [24, 26-30]. Recommendations on treatment communication (with
53 54	326	or without direct consideration of self-management support) was a strong focus in four guidelines [26-
55	327	29] and the coordination of care was addressed in more than half of guidelines [24, 26-29, 31]. Self-
50 57	328	management support was addressed indirectly in relation to individualized management in half of the
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Page 59 of 73

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# Journal of Internal Medicine

2 3	329	guidelines [26-29]. The guidelines which addressed this issue focused primarily on self-management	
4 5	330	support for medicines management and support with care coordination ( <b>Textbox 3</b> ).	
6 7	224		
8	331		
9 10	332	About here:	
11 12	333	Textbox 3: Key recommendations on individualized management	
13	334	Guiding principles	
14 15	335	<ul> <li>Use strategies for choosing therapies that optimize benefit, minimize harm, and enhance quality</li> </ul>	of
16 17	336	life for patients with multimorbidity and consider treatment burden, complexity and feasibility [2	24,
18	337	28].	
19 20	338	Consider the applicability and quality of evidence such as study population, study duration, bene	fits
21 22	339	in terms of absolute risk reduction and time horizon. Studies in younger patients without	
23	340	multimorbidity and polypharmacy and with short follow-up times and relative risk reduction may	y
24 25	341	overestimate benefits and underestimate harms, and time horizon to benefit may be too late to	
26 27	342	achieve relevant treatment effects in older patients with multimorbidity and polypharmacy [24,	28,
28	343	30].	
29 30	344	<ul> <li>In deprescribing medication(s), follow a systematic approach including identification and</li> </ul>	
31 32	345	prioritization of medicines to be discontinued, stopping one at a time and consideration of taper	ing
33	346	dosage rather than stopping, and planning and communicating with patients (and caregivers, if	
34 35 36	347	necessary) [29].	
36 37	348	• Ensure care plans are tailored to each person, giving them choice and control and recognizing th	e
37 38 39	349	inter-related nature of multiple long-term conditions [27].	
39 40	350	Health professionals involved in the treatment of patients with multimorbidity should share rele	vant
41 42	351	information about the person and their medicines – in particular when patients are transferred t	:0
43 44	352	another care setting [27, 31].	
45 46	353	Specific recommendations on clinical management	
47	354	<ul> <li>Be aware that the management of risk factors for future disease can be a major treatment burde</li> </ul>	en
48 49	355	for people with multimorbidity and should be carefully considered when optimizing care [28].	
50 51	356	<ul> <li>When prescribing medications such as statins and bisphosphonates, be aware that they may only</li> </ul>	v
52	357	provide benefit to elderly patients who have estimated survival greater than five years [30].	
53 54		[·····································	
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4	358	• The selection of a primary pharmacy is recommended to support the coordination of self-	
5 6	359	administered drugs with regard to dosage instructions and overall medication regimens, particularly	
7	360	when there are multiple prescribers [29].	
8 9	361	Ensure there is community based multidisciplinary support for patients with multimorbidity with	
10	362	social care needs which might include, for example, a physiotherapist or occupational therapist, a	
11 12	363	mental health social worker or psychiatrist, and community based services [27].	
13 14	364	Specific recommendations on self-management support	
15 16	365	Consider using an individualized patient-held medication plan that should include information on	
17 18	366	drugs and specific instruction for usage; if dosage is 'as needed', exact information about indication	
19	367	and individual dosage must be provided (single dose, interval and maximal daily dosage); in short-	
20 21	368	term prescriptions, the prospective end date should be specified and information about medication	
22 23	369	history and reduced renal function should be included when indicated [29].	
24	370	• Develop care plans that address ongoing medical and social care needs for individual patients that	
25 26	371	focus on enhancing social connectedness and community involvement and also ensuring that carers'	
27 28	372	needs are taken into consideration and that these care plans do not add to treatment burden [26-	
29	373	28].	
30 31	374	• Ensure ongoing and adequate communication, in particular around medicines and wider care plans	
32 33	375	with identification of perceived benefits and ensuring patient involvement in the process [26-28].	
34	376	<ul> <li>Consider with the person whether there are tele-healthcare options that may support them to make</li> </ul>	
35 36	377	informed choices to help them manage their conditions, as well as other potential benefits, risks and	
37	378	costs [27].	
39	379	<ul> <li>Consider the use of named care coordinators who can agree a course of action with patients and</li> </ul>	
40 41	380	their carers if these needs cannot be addressed by existing health and social care professionals. This	
42 43	381	may be particularly important at times of transition, for example when considering moving to a care	
44	382	home [27].	
45 46	001		
47	383	Toolbox	
48 49	384	Computerized decision support systems (CDSS) that support decision-making and prescribing but do	
50 51	385	not replace clinical judgment; and options for tele-healthcare [26, 27].	
52 53	386	End of Textbox 3]	
54 55	387		
56	388	Monitoring and follow-up	
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Page 61 of 73

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# Journal of Internal Medicine

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3	389	In	five guidelines, aspects of follow-up and monitoring of treatment effects as well as goal attainment	
4 5	390	we	re addressed [25-29]. Recommendations covered strategies in care planning, self-management and	
6 7	391	me	edication-related aspects, the communication with patients including patient information and safety	
8	392	ins	tructions as well as adherence, the coordination of care regarding medication appropriateness and	
9 10	393	saf	ety concerns, possible collaboration with pharmacies, the involvement of care coordinators, referra	ls
11 12	394	an	d discharge management [25-29]. Additionally, organizational or health care professionals'	
13	395	res	ponsibilities with regard to follow-up of medication-related aspects and the specific conditions in ca	re
14 15	396	ho	mes were addressed in two guidelines [26, 27] ( <b>Textbox 4</b> ).	
16 17 18	397			
19	398	[Ał	bout here:	
20 21	399	Te	xtbox 4: Key recommendations on monitoring and follow-up	
22 23	400	Gu	iding principles	
24 25	401	٠	Review and update medication / care plans regularly to recognize and record changes in needs [25	-
26	402		29].	
27 28				
29 30	403	Sp	ecific recommendations on clinical management	
31	404	•	Monitor treatment effects and clinical parameters, as well as side effects at follow-up appointment	ts.
32 33	405		Check for non-specific symptoms as potential indicators of complications resulting from treatment	
34 35	406		changes such as dry mouth, weakness / exhaustion / fatigue, drowsiness, reduced alertness, sleep	
36	407		disturbances, motor disorders, tremors, falls; constipation, diarrhea, incontinence, loss of appetite,	,
37 38	408		nausea; skin rashes, itching; depression or lack of interest in usual activities, confusion (temporary	or
39 40	409		chronic), hallucinations, fear and agitation, vertigo, tinnitus and control clinical parameters (e.g.,	
41	410		health examination, if necessary lab tests, ECG). Consider increasing the frequency of follow-up vis	its
42 43	411		following treatment changes [29].	
44 45	412	•	Monitor treatment after discharge: due to the (usually) short duration of a hospital stay, newly	
46	413		introduced medications may not have reached steady state at discharge, because inpatient care is	
47 48	414		frequently shorter than 4 to 5 half-lives of prescribed drugs. Effectiveness and side effects cannot	
49 50	415		necessarily be properly assessed in hospital [29].	
51 52	416	•	Monitor ongoing treatment including demonstrations of medication administration (e.g., inhalers)	
52 53	417		and effective forms of self-monitoring [29].	
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- 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

#### Journal of Internal Medicine

 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.

#### 462 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

477 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 

2		
3 4	508	separate production of guidelines addressing either multimorbidity or polypharmacy seems arbitrary and
- 5 6	509	their combination would also relieve the burden – for developers and users.
7 8	510	
9 10 11	511	Limitations
12	512	The systematic guideline review method offers a transparent and comprehensive approach to the
13 14	513	analysis of existing guidelines, but our in-depth text analysis may not be free from subjectivity with
15 16	514	regard to the themes selected and presented in this review.
17 18	515	
19 20 21	516	Concluding remarks
22	517	Our review identified eight comprehensive guidelines of good quality addressing older patients with
23 24	518	multimorbidity or polypharmacy. The guideline recommendations covered a broad spectrum of aspects
25 26	519	of clinical and self-management, beyond the realms of traditional disease-oriented guidelines. The
27	520	recommendations varied in their specificity – from abstract guiding principles to detailed
28 29	521	recommendations on necessary changes in practice and tools providing actionable support. The limited
30 31	522	availability of reliable risk prediction models, feasible interventions of proven effectiveness and decision
32	523	aids, as well as limited consensus on appropriate outcomes of care highlight major research deficits. An
33 34	524	integrated approach to both multimorbidity and polypharmacy should be considered in future
35 36	525	guidelines.
37 29	526	
39	520	
40 41	527	Conflict of interest statement
42 43	528	The authors have nothing to disclose.
43 44		
45 46	529	
47 48	530	Authors' contributions:
49 50	531	Drs. CM, JMV and JWB designed the concept and the program for the workshop and agreed upon with all
51 52	532	authors. Drs. CM and JWB had full access to all of the data in the study, and took responsibility for the
53	533	integrity of the data and the accuracy of the data analysis. Drs. AIGG, CM, JWB, MSB and TSN extracted
54 55	534	the data and assigned them to the Ariadne framework. Drs. AIGG, CM, JWB, SMS, MSB and TSN drafted
56 57	535	the information synthesis. Drs. CM, JWB, SMS, MET, KJ and JMV led the workshop. Drs. CM, JWB, JMV,
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59 60 536 SMS, AIGG, and MC drafted the first manuscript and all authors substantially contributed to the

537 conception, acquisition, analysis and interpretation of data, revised the manuscript critically for

important intellectual content, and finally approved it to be published. 538

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2 3	709	Figures, Tables and Web-Supplements
4 5	710	
6 7	711	Figure 1: Results of the search and selection process (flow chart)
8 9 10	712	Figure 2: Distribution of recommendations per topic and guideline
10 11 12	713	
13 14 15 16	714	Table 1: Characteristics of included guidelines
	715	Legend: *Used in 2/8 recommendations; <sup>+</sup> King's Fund definitions: Appropriate polypharmacy -
17	716	'Prescribing for an individual for complex conditions or for multiple conditions in circumstances where
18 19	717	medicines use has been optimized and where the medicines are prescribed according to best evidence';
20 21	718	Problematic polypharmacy - 'The prescribing of multiple [medicines] inappropriately, or where the
22	719	intended benefit of the [medicines are] not realized'[33]; <sup>‡</sup> Guiding principles for medicines optimization
24	720	(the Royal Pharmaceutical Society): '(1) aim to understand the patient's experience, (2) evidence based
25 26	721	choice of medicines, (3) ensure medicines use is as safe as possible, (4) make medicines optimization
27	722	part of routine practice' [32]. Abbreviations: ADR – adverse drug reaction, GoR – grade of
28 29	723	recommendation, LoE – level of evidence, MM – multimorbidity, PIM - potential inappropriate
30 31	724	medication, PP – polypharmacy
32 33	725	
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37 38	727	Web-Supplement 1: search strategy and a complete list of web-sites visited
39 40 41	728	Web-Supplement 2: list of workshop participants
42 43	729	Web-Supplement 23: list of excluded guidelines with reason for exclusion
44 45	730	Web-Supplement <u>3</u> 4: quality appraisal of included guidelines
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