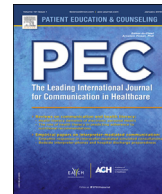




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Review Article

Methodological features of quantitative studies on medication adherence in older patients with chronic morbidity: A systematic review

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ABSTRACT

Objectives: The growing number of chronic, multimorbid older adults encourages healthcare systems to cope with polypharmacy and non-adherence. However, methodology on how to provide effective interventions to enhance medication adherence is still object of debate.
Methods: To describe methodological features of quantitative studies concerning older adults' medication adherence, by means of a PRISMA systematic review (Scopus, PubMed, Medline). A specific focus was devoted to theoretical models and to the ABC Taxonomy model, as stated by the EMERGE guidelines.
Results: 55 papers were included. Most of the studies were conducted using randomized control trials (63.6%) and focused on a single disease only (72.7%). Most of the interventions were provided by a single professional figure (70.9%). Medication adherence was mainly evaluated by means of questionnaires (61.8%) and by clinical records (30.9%). Sixteen studies considered a theoretical model in the intervention framework. The *Initiation* phase (ABC Taxonomy) was the most neglected.
Conclusions: Future studies upon medication adherence should account real-life challenges such as multimorbidity, polypharmacy and interdisciplinarity, analyzing adherence as a complex, holistic process.
Practice implications: Theoretical models may be useful to enhance the soundness of the results, to ease their comparability, to calibrate tailored strategies and to plan patient-centered interventions.

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1. Introduction

Population ageing is believed to be one of the most compelling challenges of our time [1]. In recent years and across different countries the number of people aged 65 years or over has significantly surged: the number of older adults is estimated to almost double in the next decade and even to reach 2.1 billion in 2050. In parallel, the number of people aged 80 years or over (known as the “oldest-old”) is growing even faster and it is expected to triple by 2050 [2]. Now more than ever, healthcare systems from all over the world need to cope with the urgent consequences of this ever-growing phenomenon: to deal with chronicity, multimorbidity, polypharmacy and geriatric syndromes, issues that make care a multidimensional and multifaceted mission [3–5].

In this rapidly evolving scenario, nonadherence to medications comes as a well-known public health concern [6,7]: patients who do not reach the goals of prescribed treatments may experience poor quality of life, may have low health outcomes and may require increased healthcare costs [8–11]. Nonetheless, more than 90% of older people are prescribed with drugs and almost 60% of them take five or more different medications [12]. As a result, in developed countries, nonadherence in chronic diseases ranges from 30% to 50%, and this rate is even higher in developing countries [6,13].

On this note, according to the World Health Organization (WHO), five dimensions may influence the quality of adherence outcomes, that is social and economic, healthcare system-related, therapy-related, condition-related and patient-related variables [6]. In other words, it is required to consider the complex nature of medication adherence; being a resultant of a process [14], many different factors may play an active role [8,15,16]. Several models and definitions have been proposed in literature to describe the adherence process. To date, the ABC Taxonomy represents a widely adopted framework deriving from a systematic review of behavioral and pharmaceutical studies. The model developed a quantifiable taxonomy on adherence, in order to measure parameters suitable for both scientific research and clinical practice [17]. Despite the variety of approaches, numerous efforts have been conducted in order to define the most comprehensive strategies to provide interventions enhancing adherence, but results are partially unclear, missing the gap between theory and practice [6,8,18,19].

The aim of this systematic review was to identify and describe methodological features of scientific publications on quantitative data concerning interventions aimed to improve medication adherence in the older and chronic population. The present review was encouraged by the statements listed on the EMERGE guidelines, recently developed by the International Society for Medication Adherence (ESPACOMP), (1a–1d criteria, additional criterion 3b) [20–22]. The implementation of baseline theoretical models underpinning the interventions was taken into consideration, with special reference to the ABC Taxonomy model [17,23].

2. Methods

The systematic review was registered on the PROSPERO database that was previously searched for similar reviews in order to avoid duplication: “Methodological features of quantitative studies on medication adherence in older patients with

chronic morbidity: a systematic review” (PROSPERO 2019 CRD42019129180). Data were reported according to the international PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [24] and, due to the wide heterogeneity of the methodologies adopted by the quantitative studies considered, results gathered from the PRISMA procedure for systematic reviews only will be presented. Since such a heterogeneity may have prevented reliable data analyses [25,26] the authors decided not to perform a Meta-Analysis of the results gathered.

2.1. Search strategy

An electronic literature search was performed on PubMed, Medline and Scopus databases, considering publications from January 2010 to January 2018, in order to identify interventions on medication adherence in older patients with chronic diseases. Different combinations of keywords, including *adherence, compliance, intervention, psychosocial, motivation, chronic disease/s, heart failure, hypertension, Chronic Obstructive Pulmonary Disease (COPD) and diabetes* were entered and applied in the title and abstract sections. A support from the Microsoft Office™ pack was used: after the Comma-Separated Values (CSV) files downloads from the online databases, the organization functions of Microsoft Excel were used to unify all the results in a single sheet and to remove all the duplicated records.

After the electronic search was completed, two reviewers (NG, ST) independently performed the screening of the records retrieved and subsequently identified the eligible papers (with the final supervision of AG). Doubts and concerns about inclusion and exclusion criteria were discussed through a triangulation process (NG, ST, AG).

2.2. Inclusion and exclusion criteria

Studies were considered suitable for inclusion if written in English, published by peer-reviewed journals and reporting intervention on medication adherence in samples of chronic patients with mean age ≥ 65 years. This exercise was performed in order to include target samples predominantly composed by older adults. In other words, the procedure enabled the inclusion of a broader ensemble of interventions with results extendable to the older population, even if not directly specified in the studies aim. No restrictions were made in terms of healthcare professionals or non-professional figure/s involved in the intervention (e.g. physician, nurse, pharmacist, psychologist, community health workers, peer groups, family, etc.). Furthermore, adherence to medical prescriptions had to be measurable and assessed according to the appropriate criterion [27].

Theoretical studies, protocols, reviews, meta-analysis, grey literature, qualitative studies, interventions on patients with psychiatric conditions, interventions on behavioral adherence (e.g. diet, physical activity, smoking cessation, etc.), as well as papers with no clear interventions on medication adherence, were excluded.

2.3. Data analysis through the EMERGE criteria

The EMERGE guidelines [21,22], settled and disseminated by an international multidisciplinary panel of experts, are meant to enhance the transparency and the accuracy of the scientific

reporting upon medication adherence and of the methodologies adopted [22].

For the purpose of this particular review, it was decided to focus specifically on the *additional criterion 3b*, which states the importance of implementing theoretical models for the development of the interventions on adherence and on *criteria 1a-1d*, stressing the need of the implementation of the ABC Taxonomy model in all its three phases [22].

A first section of the present systematic review was focused on the retracement of theoretical models in the intervention's methodology. Afterward, information from the articles included was analyzed through the lenses of the ABC Taxonomy [17,23]. The model conceptualizes adherence to medications according to the principles of behavioral and pharmacological science and it divides the process of being adherent into three subsequent phases. Such phases represent a sequence of events that need to occur in order to achieve the best results from the prescribed treatment: (a) "Initiation, which occurs when the patient takes the first dose of a prescribed medication"; (b) "Implementation, which indicates the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from Initiation until the last dose is taken"; (c) "Persistence, which corresponds to the time elapsed from the Initiation phase, until the eventual treatment discontinuation" [23].

Namely, the three subsequent ABC taxonomy phases were applied as a step-by-step reference, guiding the methodology analysis of the papers included.

Three reviewers (NG, ST, AG) firstly established if the ABC Taxonomy was explicitly considered by the interventions included. If not, the authors determined if the interventions were developed implicitly considering the subsequent phases highlighted by the model. The content analysis, similarly, with the paper screening phase, was structured by means of a triangulation process: the reviewers independently marked the presence (or the absence) of each one of the three ABC Taxonomy phases by looking through the intervention rationales and according to ad-hoc criteria:

(a) *Initiation* - marked if the intervention framework was developed taking into account the start of a new medication; (b) *Implementation* - marked if the intervention was focused on following the correct dosage and timing of a specific medication intake; (c) *Persistence* - marked if the intervention was provided in order to sustain proper medication adherence overtime.

The degree of agreement has been determined alongside by NG, ST and AG through a data matrix. Each reviewer involved in the process (NG, ST, AG) had to mark the presence or the absence of the ABC Taxonomy phases in the studies considered. A final supervision has been performed by all the authors until a full consensus was reached.

2.4. Data extraction

Information collected through the full-text analysis was organized in a synoptic table (*Appendix A*), according to the following categories: [A] *Study characteristics*: first author, publication year and study design; [B] *Study participant's characteristics*: sample size, mean age and type of disease/s; [C] *Geographical and socio-economic characteristics*: nation of the study and nation ranking according to the Human Development Index (HDI) [28]; [D] *Intervention features*: setting, healthcare professional or non-professional figures involved, the eventual presence of family/caregiver involvement in the intervention framework, intervention classification, as reported in a recent literature review [29], and duration/follow up; [E] *Medication adherence*: evaluation criteria [27] and the eventual presence of other evaluated outcomes (self-care behaviors, quality of life, treatment satisfaction, etc.). Macro-categories [D] and [E] share one sub-category that outlines the

eventual presence of Information Communication Technologies (ICT) [30] both in the intervention framework and/or as evaluation tool (e.g. Medication Event Monitoring Systems). [F] Data analysis through the EMERGE criteria: The eventual presence of theoretical models in the intervention frameworks and the content analysis according to the ABC taxonomy phases [17,23]. [G] *Medication adherence-related outcomes*.

3. Results

After database searching and duplication removal, 2633 records were found. Following the title/abstract screening, 286 suitable articles were found and after the full-text reading, 55 studies were included in the systematic review. Most of the excluded records were not focused on medication adherence ($n=824$), did not include interventions ($n=401$) or provided interventions on behavioral adherence only ($n=375$) (Fig. 1). The information collected is represented in a synoptic table (*Appendix A*) [31–85]. The total number of patients of the included studies was 120,727 and the sample sizes varied widely, ranging from 10 patients to 39,017 patients, with most of the studies including more than 100 patients (70.9%) (mean age range: from 65 ± 13.3 to 81.46 ± 5.7 years).

Tables 1a–1c summarize the results concerning the nations of the studies, the adopted study design, the type of disease/s, the interventions classification, settings and professional figures involved in the interventions, as well as medication adherence evaluation criteria, the eventual presence of ICT in the intervention and/or in the adherence evaluation process, as well as the presence of other relevant outcomes. Tables 1a–1c show that studies were conducted mostly in the USA (47.3%), with more than half of the interventions provided with a Randomized Controlled Trial (RCT) design (63.6%) and most of the studies focused on the management of a single disease only (72.7%). As to interventions, they were mainly provided through Patient Education (54.5%) [29], in a single setting (78.2%), by a single professional figure (70.9%) and in the 56.4% of the cases with the support of an ICT. Concerning medication adherence, it was mostly evaluated by a single method/criterion (78.2%) and ICT were used in the 47.3% of the cases to support the adherence evaluation phase. Considering other relevant outcomes, more than a half of the studies (67.3%) evaluated additional aspects beyond medication adherence, such as self-care behaviors (34.5%), including diet, physical activity, smoking cessation and monitoring of clinical values.

Furthermore, the analysis focused also on identifying the possible involvement of family and caregivers in the interventions. Results showed that only five studies [42,50,65,67,69] combined family involvement with the intervention as a support to achieve patients' adherence goals.

As to the data analysis through the lenses of the EMERGE criteria, sixteen studies considered a psychological theoretical model in the intervention framework: the Motivational Interviewing model [86,32,36,50,57,64,66,73–75], the Health Belief Model [87,50], the Self-efficacy theory [88,79], the Self-regulation theory [89,67,70], the Health Collaboration Model [90,76], the Five As model [91,60] and the 4Cs model [92,81]. The ABC Taxonomy's phases [17,23] were implicitly considered by all the studies; the majority of the interventions presented the *Implementation* with *Persistence* phases only (85.5%) and the 14.5% [41,44,47,48,52,70,80,83] focused on all the three ABC Taxonomy phases altogether (*Initiation*, *Implementation*, *Persistence*).

Finally, concerning the medication adherence outcomes, the 47.3% of the studies reported a significant pre-post improvement [31,32,34,39,41,44–46,49,51,52,54,55,58,59,64,66,67,70,72,74,76,81,82,84,85].

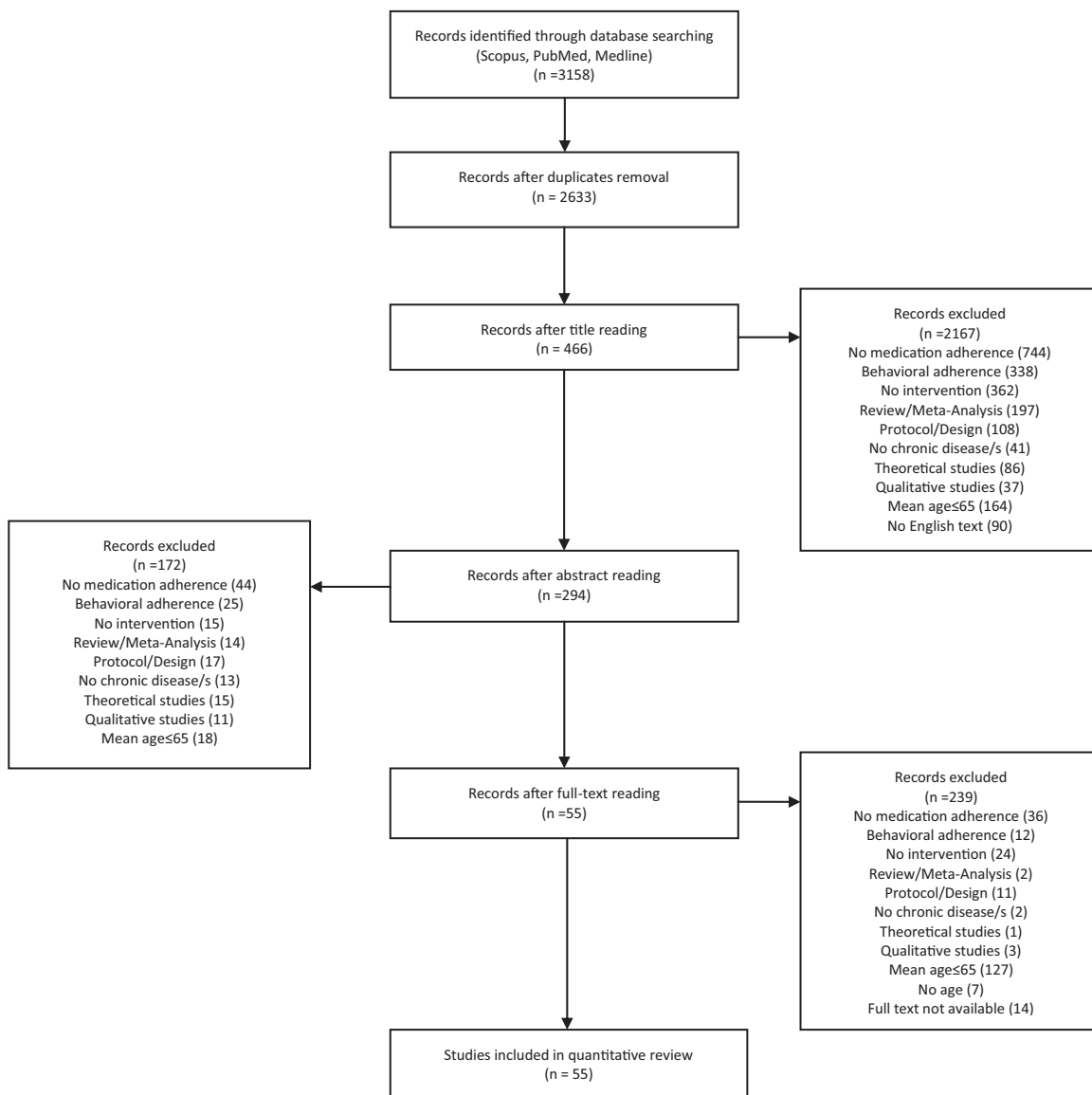


Fig. 1. PRISMA Flow Diagram of the systematic review.

Table 1a
Main features of the studies included (n = 55).

Nation	HDI° (Ranking)	n (%)	Study design§	n (%)*	Disease/s	n (%)*
USA	0.920 (15)	26 (47.3)	Randomized controlled trial	35 (63.6)	Hypertension	21 (38.2)
United Kingdom	0.920 (15)	5 (9.1)	Clinical trial (single group, pre-post design)	12 (21.8)	Diabetes	18 (32.7)
Spain	0.893 (25)	4 (7.3)	Non-randomized controlled trial	5 (9.1)	Heart Failure	11 (20)
Australia	0.938 (6)	3 (5.5)	Retrospective study	3 (5.5)	Chronic Obstructive Pulmonary Disease	5 (9.1)
China	0.758 (85)	3 (5.5)			Chronic diseases	5 (9.1)
South Korea	0.906 (22)	3 (5.5)			Glaucoma	2 (3.6)
Brazil	0.761 (79)	2 (3.6)			Asthma	1 (1.8)
Denmark	0.930 (11)	2 (3.6)			Chronic Kidney Disease	1 (1.8)
Portugal	0.850 (40)	2 (3.6)			Osteoporosis	1 (1.8)
Argentina	0.830 (48)	1 (1.8)				
Austria	0.914 (20)	1 (1.8)				
Canada	0.922 (13)	1 (1.8)				
India	0.647 (129)	1 (1.8)				
Netherlands	0.933 (10)	1 (1.8)				
					Single disease	40 (72.7)
					Multiple diseases	15 (27.3)

° HDI index is based on 3 dimensions: (a) Life expectancy at birth; (b) Expected years of schooling and mean years of schooling; (c) Gross National Income per capita (United Nations Development Programme, <http://hdr.undp.org/en>. Accessed on December 2019).

Table 1b
Intervention features of the studies included (n = 55).

Intervention type [^]	n (%) [*]	Setting	n (%) [*]	Healthcare professionals	n (%) [*]	Information communication Technology (ICT)	n (%) [*]
Patient Education	30 (54.5)	Patient's home	29 (52.7)	Pharmacist	23 (41.8)	Telephone calls	19 (34.5)
Clinical Pharmacist Consultation	17 (30.9)	Outpatient setting	23 (41.8)	Nurse	19 (34.5)	Electronic reminder systems	7 (12.7)
Cognitive Behavioral Therapy	11 (20.0)	Pharmacy	8 (14.5)	Physician	17 (30.9)	E-mail, SMS, Fax	5 (9.1)
Medication-taking Reminders	9 (16.7)	Inpatient setting	5 (9.1)	Researcher	7 (12.7)	Tele-monitoring	5 (9.1)
Incentives to Promote Adherence	3 (5.5)	Community Center	2 (3.6)	Educator	3 (5.5)	Interactive Voice Responder	2 (3.6)
Medication Regimen Management	1 (1.8)			Clinical provider (not specified)	1 (1.8)	PC, Tablet, Smartphone Application	2 (3.6)
				Community health worker	1 (1.8)		
				Non-professional figure	1 (1.8)		
				Social worker	1 (1.8)		
				Technician	1 (1.8)		
		Single setting	43 (78.2)	Single professional figure	39 (70.9)	Presence of ICT	31 (56.4)
		Multiple setting	12 (21.8)	Multidisciplinary team	16 (29.1)	Absence of ICT	24 (43.6)

Table 1c
Evaluation features of the studies included (n = 55).

Adherence evaluation method	n (%) [*]	Information Communication Technology (ICT)	n (%) [*]	Other evaluated outcomes	n (%) [*]
Self-reported measures	34 (61.8)	Clinical/Pharmacy records	17 (30.9)	Self-care behaviors ^b	19 (34.5)
Clinical/pharmacy records ^a	17 (30.9)	MEMS	8 (14.5)	Quality of life	13 (23.6)
MEMS	8 (14.5)	Telephone calls	3 (5.5)	Clinical outcomes	12 (21.8)
Pill count	6 (10.9)	Pc, Tablet, Smartphone Application	1 (1.8)	Patient's satisfaction	9 (16.4)
Clinical values	1 (1.8)			Self-efficacy	5 (9.1)
				Hospital admissions	4 (7.3)
				Mental health	1 (1.8)
				Social support	1 (1.8)
Single method	43 (78.2)	Presence of ICT	26 (47.3)	Presence of other evaluated outcomes	37 (67.3)
Multiple methods	12 (21.8)	Absence of ICT	29 (52.7)	Absence of other evaluated outcomes	18 (32.7)

^{*}Refers to the absolute frequency and percentage of each single category retrieved in the included studies (for further details see Appendix A). [^] as reported in: Kini et al. [29][§] Clustered categories according to the included study characteristics (for further details see Appendix A).

^a Including Medication Possession Ratio (9.1%), Medication refills (1.8%), Proportion of Days Covered (14.5%) and Time to Treatment Discontinuation (1.8%).

^b Including diet, physical activity, smoking cessation and monitoring of clinical values.

MEMS, Medication Event Monitoring Systems.

4. Discussion and conclusions

4.1. Discussion

The results collected through this systematic review led to the identification of different issues concerning the methodological features of the interventions on medication adherence in patients with chronic morbidity. In particular, the implementation of theoretical models underpinning the interventions was considered, and it will be furtherly discussed in a dedicated section (see paragraph 4.1.1).

Overall, although representing a global demanding challenge, medication adherence resulted to be mainly accounted in western and highest HDI regions of the world. Accordingly, the study results need to be considered with caution, since there might be a risk of bias in generalizing the results, especially when comparing low HDI versus high HDI countries.

Available literature points out that the prevalence of multi-morbidity increases with age and it is present in most people aged 65 years and older [93–96]. Such epidemiological changes are proved to affect the older population in terms of health-related quality of life [97] and they currently determine a significant peak in the economic burdens of health care systems [98]. Interestingly, despite the prevalence of reliable methodologies in the design of the studies included (RCT were mostly used on the purpose), the

largest part of the interventions resulted to be focused on single chronic conditions. Hence, it is highly advisable to drive attention towards newest strategies able to collect sound and multi-level information upon multimorbidity, particularly given the urgency connected to its management in long-term care [94,99] and the possible negative implications of rising rates of polypharmacy, which may result in compromised safety [100].

Concerning the Intervention Type, Patient Education resulted the most prevalent methodology being used in the studies included, alone or in combination with other methods [33,35,37,44,46,48,50,51,59,66,73,74,84]. It is worth noticing that, as stated by Kini and colleagues [29], Patient Education has shown modest success in improving adherence. Combinations of different methodologies may, on the other hand, help increasing medication adherence rates.

With regard to the intervention settings, results showed a prevalence of interventions lead in home-based and outpatient settings, highlighting the importance of the continuity of care. It may be of interest to enhance the number of interventions conducted in inpatient settings, in order to successfully bridge the gap that links the patient's journey from hospital to home.

As for the necessity to collect multi-level variables, more than half of the interventions were mastered, instead, by a single healthcare professional figure. Although the lack of consensus upon the most effective approach on multidisciplinary

interventions [101,102], the evidence about the positive role of multiprofessional teams is currently growing and related methods are increasingly applied in literature [4,5,103]. Accordingly, it is to be encouraged the creation of interprofessional settings, in order to establish comprehensive, holistic and patient-centered approaches to medication adherence [104]. Namely, it may be useful to start developing an integrated methodology, merging core competences coming from different professional backgrounds (e.g. physician, nurse, pharmacist, community health worker, social worker, etc.). These adjustments may be useful both for the sake of clinical practice and for tailoring frameworks able to guide future research, within the need to closely guide patients before, throughout and after receiving the medication prescription. On this topic, caregivers and family represent a powerful resource to sustain the daily burdens of properly taking medications [6]. Interestingly, findings showed that only few studies [42,50,65,67,69] integrated family involvement in the intervention framework. Relatives and informal caregivers were engaged, for example, to support patients' medication adherence goals or to supervise patients when using technological supports. In other words, it appears to be a lack of quantitative data about family and caregiver involvement in the management of medication adherence [105]. Indeed, patients act in a multilevel environment in which several factors are constantly interacting and influencing adherence outcomes (e.g. family, caregivers, acquaintances, etc.) [106]. To the best of our knowledge, few studies have been conducted focusing on psycho-social factors involved in the medication adherence process and a full consensus was missing [107]. Thus, it is suggested to further investigate in future studies the role of family and social factors in the handling of medication adherence.

Regarding the evaluation of medication adherence, a variety of methods have been used (ICT included). Indeed, few studies used a combination of different methodologies during the evaluation phase [40,44,47,48,50,54,57,61,63,65,74,83]. Furthermore, a triangulation of two or more different methods was not systematically applied [108], preventing the possibility to measure adherence according to different perspectives and to enhance the reliability of the outcomes [27]. Recent studies underlined the importance of triangulation among different techniques while measuring adherence [27,108]. These findings could represent a potential limit of the studies included in this review, since the use of one single criterion in evaluating adherence may result in biases of under or overestimation, especially if only questionnaires or self-reported measures were administered [109]. Similar observations are reserved to the evaluation by means of ICT, characterized by a prevalence of pharmacy records and MEMS; although they are considered a more reliable strategy to evaluate medication adherence [27], it was observed lack of triangulation among different methodologies.

Concerning the ICT implementation for the betterment of medication adherence, the wide adoption of telephone calls is probably due to their feasibility, cost-effectiveness and their compatibility with the healthcare routine. Also, telephone calls keep the relation with healthcare professionals and offer patients the possibility to provide prompt feedbacks on their own experience [147]. Furthermore, the efficacy of telephone follow-up interventions in easing care costs and enhancing medication adherence and patients' beliefs about medicines, has been recently examined [110]. Still, older patients could be concerned when approaching to complex technological supports (i.e. smartphones, tablets and other devices) [111]. Given the ongoing advances in technology, such barriers deserve to be furtherly discussed in literature during the forthcoming years. Moreover, specific interventions should be designed to enhance ICT literacy of older adults and to guide technology companies in creating user-friendly ICT tools, suitable for this specific population.

4.1.1. Considerations stemming from the data analysis based on the EMERGE criteria considered

According to the data analysis with the EMERGE criteria, it is interesting to bring into notice the low prevalence of baseline theoretical frameworks able to guide the methodological assumptions of the interventions (*additional criterion 3b*). Therefore, a dedicated space for reflection upon theories underpinning a study protocol is, indeed, generally missing. Except for the sixteen articles reported in the results section [32,35,36,50,57,60,64,66,67,70,73–76,79,81], adherence to medication was exclusively defined operatively and/or indirectly, by means of the instruments applied (e.g. questionnaires, pill count, etc.), with no reliance to conceptually validated definitions (e.g. WHO definition) nor to theoretical models, such as, for instance, the ABC Taxonomy [17,23].

Furthermore, the content analysis regarding the ABC Taxonomy showed a general neglect of the *Initiation* phase. Indeed, the result may reflect the sample characteristics of the studies, as interventions were provided to samples mainly composed of older people, which may be suffering from a chronic condition from many years. Similarly, patients might have the same medication therapy since when their illness was first diagnosed, with slight variations on timing and dosage, thus preventing the possibility to evaluate implications related to the very first commitment to therapy. Despite the actual characteristics of the sample and given the implication in terms of public health expenditures, primary non-adherence remains a sensitive issue deserving urgent attentions from the healthcare systems worldwide [13].

On the other hand, interventions reviewed principally focused on the *Implementation* and *Persistence* phases altogether. In our opinion, this result reflects the peculiar nature of these two phases; healthcare professionals provided interventions on both the phases at the same time, focusing on a combination of strategies either referred to *dosage*, *timing* and *duration* as different aspects of the same practical matter. The merging of these two phases could be phrased as “properly taking a medication for the required period of time”, which essentially represents what the patient is required to do with his/her medication on a daily basis. Hence, despite the ABC taxonomy theoretically considers *Implementation* and *Persistence* as different and separated moments of the adherence process, in order to achieve improvements on medication intake they are required to be managed jointly, as overlapping stages. Further research could be performed in order to verify the soundness and the implications of these considerations.

Indeed, results coming from this process may provide a guiding approach for determining contents of interest when it comes to analyzing medication adherence and its facets. Furthermore, the adoption of the EMERGE guidelines could enhance interventions soundness and convey best-practices to program structured interventions.

Lastly, even though the focus of the present review relied exclusively on adherence to medications, different interventions were provided considering behavioral adherence and lifestyle changes as well [33,39,40,47,51,59,63,65–67,70,72,74,75,77,79,81,82,85]. These data outline a considerable attention on healthy behaviors, promoting patients' active role in their therapeutic self-management by means of skills development and supporting tools [104]. On this purpose, the WHO and the European Union published indications for the forthcoming years, stressing the importance of an active and healthy ageing in order to maximize older adults' functional ability [112,113].

Along with the patient's active role, another aspect that deserves to be stressed is treatment satisfaction. In this regard, only nine studies [35–37,42,43,55,59,62,81] reported treatment satisfaction as a secondary outcome (see *Appendix A*). This data highlights the presence of few interventions on chronic diseases that consider the evaluation of patients' satisfaction as an

informative event [114]. Such an aspect should be an essential strategy to promote medication adherence, especially referring to the growing interest in Patient-Centered Approaches [104], and to the active patient's role along in the management of medication adherence. In this regard, Patient-Reported Outcome Measures [115] are gaining a significant attention in literature given their close connection to topics such as precision medicine and patient and outcome-centered approach [116]. Conclusively, the topics here discussed may provide other interesting cues upon methodological features to be considered in studies aiming at enhancing intervention on adherence.

4.2. Limitations and strengths

Some limitations of this review need to be detailed. Firstly, it has been decided to omit psychiatric conditions or comorbidities in the papers' screening phase. Indeed, the decision led to overlook a sensitive facet related to non-adherence, with peculiar repercussions in older patients with chronic morbidities. Nevertheless, studies on the matter suggests that psychiatric illnesses, if compared to other chronic diseases, seem to require ad-hoc intervention strategies [117], such as the implementation of different and tailored behavioral techniques [118]. Still, given the possible data heterogeneity, it may be crucial to further investigate this topic, in order to deepen potential differences among these populations. A Systematic Review should be performed and future studies investigating the effect of psychiatric illnesses on patterns of medication adherence may be advisable. With regard to the exclusion criteria, having excluded grey literature may have led to miss relevant studies from eastern world/low-income countries. Parallely, since medication adherence resulted to be mainly investigated in the western regions of the world, another limitation concerns the possible risk of bias in generalizing the results of the present research.

As for the method section, the methodology adopted to trace the ABC Taxonomy phases in the methodology may have led to idiosyncratic attributions, as a qualitative approach was applied. Despite that, the full consensus reached at the end of the process is promising, and the final supervision made by experts of different disciplines may have helped avoiding biased results.

4.3. Conclusions

The present effort sheds light on the most common strategies used to measure and intervene on medication adherence in chronicity, providing cues for the forthcoming researches aiming at exploring the same matter. Future studies upon medication adherence should include an adjusted focus upon the real-life implementation of the intervention adopted, taking into account recent epidemiological trends. Issues such as multimorbidity and polypharmacy among older adults need to be enclosed as well, analyzing adherence according to complex patterns of conditions rather than to single illnesses. Moreover, context variables are to be actively integrated into the plan (e.g. multi-professional teams, family, caregiver assistance, social barriers evaluation, etc.) to collect holistic and multi-level information, useful for calibrating tailored strategies and to plan reliable, comprehensive, feasible and patient-centered interventions.

4.4. Practice implications

The quantitative interventions considered were particularly heterogeneous in terms of measurements and strategies implemented and they were not often relying on a specific theoretical framework. Indeed, theoretical models may be of use to help gathering and integrating the complexity of the variables that

characterize the adherence process. Also, a reliance upon the EMERGE guidelines may help researchers while structuring and reporting results on quantitative data, enhancing the soundness of the results and easing their comparability, for the ongoing betterment of the intervention outcomes. Moreover, data concerning medication adherence outcomes should be weighed considering the combination of evaluation and intervention methodologies administered by the researchers. In this regard, future studies should always evaluate and intervene on medication adherence through multiple procedures, for more reliable results. Finally, further investigations on self-care behaviors, family support, quality of life, patient's satisfaction, might add useful complementary information to manage the complexity of the process.

Author contributions

All authors contributed to the study design and conception. NG was responsible for data acquisition in this review. NG, ST, AG contributed to data analysis and drafted the manuscript. PK, EC, MKM, and LM critically revised the manuscript providing relevant suggestion. All authors gave their approval on the final version of the manuscript.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.pec.2020.04.006>.

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