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Involvement in medication safety behaviors among older people with chronic diseases: systematic review of intervention studies

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Abstract

Background This study aimed to systematically evaluate interventions and effects that promote involvement in medication safety among older people with chronic diseases and to provide new ideas and references for developing standardized and effective intervention strategies to improve patient involvement in medication safety.

Methods A comprehensive literature search across twelve databases was conducted using both computerized and manual methods. The search was limited to studies designated as randomized controlled trials or quasi-experimental studies and was conducted from the time of each database's inception until September 2023. Two researchers independently carried out qualitative analyses, which included screening the literature, extracting the data, and assessing the quality of the selected studies.

Results This study included five studies involving a total of 388 participants, with interventions aimed at enhancing patient involvement in medication safety, including interactive health education, motivational interviewing, and medication reconciliation. However, direct evidence confirming the positive impact of these interventions in promoting medication safety behaviors among older people with chronic diseases is still lacking.

Conclusions Patient involvement in medication safety behaviors is essential for promoting healthy aging. Medication education, motivational interviewing, and medication reconciliation may improve the willingness and ability of older people to participate. However, limitations in the methodological quality of current studies prevent drawing definitive conclusions, highlighting the urgent need for more high-quality research.

Trial registration PROSPERO number CRD42023494924.

Keywords Older people, Chronic diseases, Patient involvement in medication safety, Patient involvement, Systematic review

Background

According to the 2022 United Nations World Population Prospects report [1], the global population aged 60 and above in 2021 was 1.083 billion, with China accounting for approximately 23.8%, equivalent to approximately 258 million people. The aging population has led to a significant increase in the burden of chronic diseases. Statistics indicate that the prevalence of multiple chronic diseases among Swiss individuals aged over 65 years exceeds 60%, with more than 50% of patients experiencing three or

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more chronic diseases [2]. Pharmacological therapy is the primary method for managing chronic diseases. Older people with chronic diseases in places such as Europe and Lebanon typically require concurrent use of five or more medications, with the percentage ranging from 45.2% to 71.8% [3, 4], with an average daily frequency of four administrations [5]. This regimen includes high-risk medications necessitating monitoring and dosage adjustment, such as hypoglycemic, antihypertensive, and cardiovascular agents. Nevertheless, China's older people frequently demonstrate unsafe medication practices, including adjusting medication types, dosages, and frequencies (63.63%), self-discontinuation of medication based on symptom improvement or worsening (53.8%), forgetfulness in medication adherence (48.7%), irregularity or omission of doses (44.1%), failure to adhere to medication monitoring schedules (43.75%), and errors in timing or substitution of medications (18.81%) [6–8]. These unsafe medication behaviors can predispose older people to safety incidents, including falls, cognitive decline [9], while also diminishing the efficacy and safety of medications and escalating the national financial burden (global costs attributed to medication errors are estimated at 42 billion US dollars annually) [10–12].

Each individual bears primary responsibility for their health. The "Global Patient Safety Action Plan 2021–2030" [13] and the "Healthy China Action (2019–2030)" [14] advocate that the public enhance their proactive health consciousness and actively engage in self-care and health practices. In 2022, the patient safety advocate Helen Haskell introduced "Patient Involvement in Medication Safety" during a series of drug safety network seminars held by the WHO, emphasizing the core role of patients in ensuring medication safety [15]. "Patient involvement in medication safety" is a strategy for reducing medication injury and errors and is characterized by being "patient-centered" [16] and "personalized" [17], with studies primarily focusing on countries such as the United Kingdom [18–20], the United States [21–23], and Australia [24–26]. Currently, there is no unified definition of the term "patient involvement in medication safety". Wang Binghan [27] described that patient involvement in medication safety refers to actions taken by patients with independent decision-making abilities to promote the safe, rational, and effective use of medication before, during, and after receiving standard medical treatments. "Patient involvement in medication safety" has been proven to fully mobilize the enthusiasm and initiative of patients and effectively reduce medication errors [13]. For instance, Zhang Huiling [28] implemented a phased and progressive patient involvement in medication safety management plan for older people with cardiovascular conditions at home, tailored to their varying medication needs at different stages. This approach effectively raised patients' awareness of and engagement in medication safety management, encouraging them to take an active role in ensuring their own medication safety. However, research on safeguarding patient medication safety from the perspective of "patient involvement" is still in its infancy. Although there has been some practice in medication education for older people with coronary heart disease and diabetes, there is still insufficient direct evidence to prove the effectiveness of "Patient involvement in medication safety." Existing studies have yet to clarify the specific impact and implementation methods of such interventions, and significant uncertainty remains about how to effectively encourage older people to actively engage in medication safety.

This study aimd to systematically evaluate interventions to improve participation in medication safety behaviors among older people with chronic diseases, providing new ideas and references for the development of subsequent intervention plans and research.

Research design and methods

The study was conducted from June 2023 to January 2024 and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To complement and extend the PRISMA protocol, we used the Synthesis Without Meta-analysis in the Systematic Reviews Checklist recommended by the EQUATOR network ("Enhancing the Quality and Transparency of Health Research"; www.equator-network.org) [29]. Registered as PROSPERO CRD42023494924. The systematic review was performed based on the following stages: (a) defining suitable keywords, (b) finding and selecting studies and articles in different databases, (c) critical evaluation of these studies, (d) data selection and analysis, and (e) presentation and interpretation of the results.

Search strategy

A comprehensive search, both computerized and manual, was conducted across 12 electronic databases, encompassing PubMed, Web of Science, CENTRAL, CINAHL, Medline, EMBASE, Ovid, PsycINFO, CNKI, WanFang Data, CBM, and VIP. This search extended from the inception of each database to September 2023. A combination of subject terms and free terms was used and adapted to the characteristics of each database. Additionally, the references of the included studies were also searched, and relevant information was obtained through snowballing. The search terms used were "aged/elderly/older people, patient participation/patient engagement/patient involvement/patient empowerment/patient activation/shared decision-making/person-centered care/person centered/patient focused, medication

management/medication self-management/safety medication, intervention/application/impact/effectiveness and randomized controlled trial/controlled clinical trial/random*/placebo*/trial/groups". The full search strategy, using PubMed as an example, is provided in Additional file 1: Appendix 1.

Eligibility criteria

The inclusion criteria for the study were delineated using the PICOS format, as detailed below: P (population): older people with chronic diseases (aged 60 years or older) [30]; I (intervention): patient involvement or patient involvement in medication safety as the main intervention strategy, without restricting the others for the time being; C (control): including a blank control, routine control, among others; O (outcome): patient involvement in medication safety behaviors and positivity; and S (study design): requiring the inclusion of randomized controlled trials or quasi-experimental studies. The Exclusion criteria were non-Chinese and non-English literature, reviews, case reports, qualitative research, conference papers, and those with incomplete data, inaccessible full texts, or redundant publications. Any study that met one or more of the above criteria was excluded. The intervention criteria examples can be found in Additional file 2: Appendix 2.

Study selection and data extraction

Two researchers independently conducted literature screening and data extraction, with a third researcher assisting in judgment in case of disagreement. The initial search results were deduplicated using EndNote 20 software. Subsequently, titles and abstracts of the literature were reviewed to exclude clearly irrelevant studies, followed by a thorough evaluation of the full texts to assess their eligibility against the inclusion criteria. Additionally, the references of the included studies were supplemented using the snowballing method. Where necessary, the authors of the original studies were contacted by email and telephone to acquire information that was not identified but was important for this study.The following data were extracted using standardized tables: first author and year of publication; country; study design; study population; total sample size and dropout rate; elements of the intervention (intervention measures, intervention frequency, intervention period, intervention duration, etc.); study setting; time of evaluation; outcome indicators and research tools; and study results.

Risk of bias in individual studies

The quality assessment of the included randomized controlled trials (RCTs) was performed according to the protocol established in the Cochrane Handbook 5.1.0 [31]. This approach included random allocation, allocation concealment, blinding of implementers and participants, blinding of outcome assessors, complete reporting of data, selective reporting of results, and other sources of bias, such as sample size estimation and baseline comparability, and offered three ratings for each item: "low risk of bias," "high risk of bias," or "unclear." Original studies were assigned a quality rating of A if all the above criteria were fully met, B if the criteria were partially met, and C if they failed to meet the criteria entirely.

For the quality assessment of quasi-experimental studies, the MINORS scale [32], which comprises 12 items, was used. Each item was scored from 0 to 2, with 0 indicating nonreporting, 1 indicating reporting insufficient information, and 2 indicating reporting and providing sufficient information.

The literature evaluation process was independently conducted by two researchers, and any disagreements were resolved through discussion. A third researcher was consulted if an agreement could not be reached.

Data synthesis

A narrative synthesis method was used due to the considerable variation between the study designs of the included studies.

Results

Study search and selection

In this study, a comprehensive systematic search across 12 domestic and international electronic databases yielded a total of 1,385 records: PubMed ($n=148$), Web of Science ($n=196$), CENTRAL ($n=716$), CINAHL ($n=36$), MEDLINE ($n=67$), Ovid ($n=124$), Embase ($n=29$), PsyINFO ($n=10$), CNKI ($n=32$), Wangfang Data ($n=9$), VIP ($n=12$), and CBM ($n=6$). After removing duplicates ($n=152$) using EndNote 20 software, the titles and abstracts of the literature were read for screening ($n=1233$), and 1189 records were excluded from the list of records that were completely irrelevant to the study topic ($n=1087$), nonpatient involvement in medication safety interventions ($n=21$), qualitative research ($n=28$), reviews ($n=14$), repeated publications ($n=2$), and other nonconformities ($n=37$). A full-text search of potentially relevant literature was conducted ($n=44$), and the literature was selected against the inclusion criteria, resulting in a review of five intervention studies, where other sources ($n=3$) were derived from the reference lists of the included studies. The literature review screening process is summarized in Fig. 1.

Quality assessment

The evaluation of the literature quality is presented in Tables 1 and 2. The quality of evidence from the four

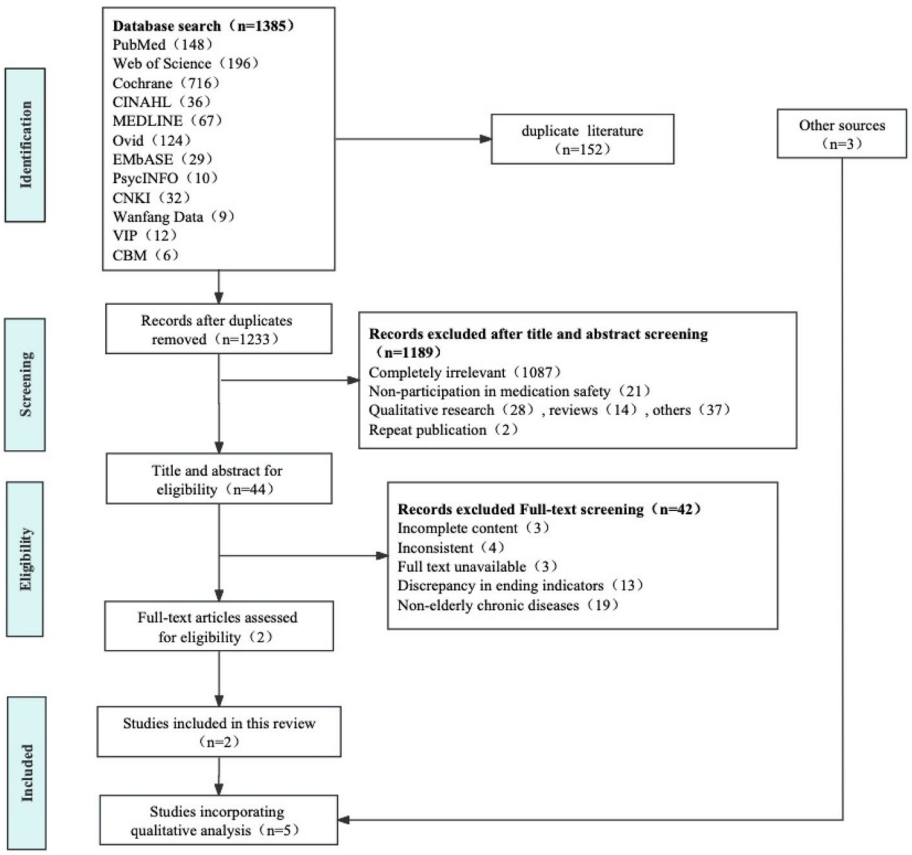

Fig. 1 Flow diagram of the literature screening process

Table 1 Quality assessment of the included RCTs

Inclusion of studies	Random allocation	Allocation concealment	Blinding		Outcome data integrity	Report bias	Other bias	Evidence quality
			Study subjects/ interveners	Outcome assessors				
Hochhalter [33]	Low risk of bias	Unknown	Unknown	Unknown	Unknown	Low risk of bias	Low risk of bias	B
Jiayi Mao [34]	Low risk of bias	Low risk of bias	Unknown	Unknown	Low risk of bias	Low risk of bias	Low risk of bias	B

Table 2 Quality assessment of the included quasi-experimental studies

Inclusion of studies	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	Total score	Evidence quality
Huiling Zhang [28]	2	1	0	1	0	1	0	0	0	2	2	2	11	C
Xiaodan Niu [35]	2	1	0	2	0	1	0	2	2	2	2	2	16	B
Na Li [36]	2	1	0	2	0	1	0	2	2	2	2	2	15	B

included articles received a rating of B, and one was rated as C, signifying that the included studies carried a moderate to high risk of bias.

Studies and participants

Basic data extraction details are provided in Table 3. We included five studies [28, 33–36], comprising one

Table 3 Basic information of included literature

First author and year of publication	Country	Type of intervention	Study population	Total sample size(cases) and dropout rate	Elements of intervention	Study setting	Data collection time	Outcome indicators (research tools)	Study results
Hochhalter [33] 2010	America	RCT	Older people with chronic diseases	*N* = 79 (64) Intervention group = 26 (20) Control group = 26 (21) Safety group = 27 (23) Dropout rate = 18.98%	**Intervention group:** patient involvement intervention Intervention period: n/a Interventio frequency: n/a Interventio duration: 1 seminar 2 h, 2 telephone follow-ups 15 min Intervention components: seminar/telephone follow-up **Control group:** routine care	Large internal medicine clinics	Baseline End of 6th month postbaseline	Positivity: PAM-13 Self-efficacy: Chronic Disease Management Self-Efficacy Scale	No expected improvements in patient positivity, self-efficacy, etc., from patient involvement were found
Huiling Zhang [28] 2017	China	Quasi-experimental study	Older people with cardiovascular disease	*N* = 120 (104) Intervention group = 60 (49) Control group = 60 (55) Dropout rate = 13.33%	**Intervention group:** patient involvement in medication safety management Intervention period: 12 weeks Intervention frequency: 1 ~ 2 weeks 1 home visit, 30 ~ 60 min each time Intervention components: health education/motivational interview/telephone follow-up/home visit **Control group:** routine education	Home + community health centers	Preintervention Immediately postintervention End of 1st month postintervention End of 3rd month post- intervention	Medication bias: Medication Error Questionnaire Self-efficacy: SEAMS Positivity: PAM-13	There was no statistically significant medication bias after 3 months of intervention. There was a tendency for self-efficacy to decrease over time. The total positivity scores of all patients in the intervention group were greater than the total positivity scores of patients in the control group

Table 3 (continued)

First author and year of publication	Country	Type of intervention	Study population	Total sample size(cases) and dropout rate	Elements of intervention	Study setting	Data collection time	Outcome indicators (research tools)	Study results
Xiaodan Niu [35] 2021	China	Quasi-experimental study	Older people with type 2 diabetes mellitus	*N* = 81 (71) Intervention group = 42 (36) Control group = 39 (35) Dropout rate = 12.35%	**Intervention group:** medication reconciliation Intervention period: hospitalization + 3 months follow up Intervention frequency: variable Intervention components: medication reconciliation /health education **Control group:** health education	Endocrinology Department + phone/ WeChat	Day 7 postdischarge End of 1st month postdischarge End of 2nd month postdischarge End of 3rd month postdischarge	Medication bias: Medication Bias Assessment Tool Self-efficacy: SEAMS Engaging in Medication Safety Behaviors: MMAS-8 Blood glucose	At 3-month follow-up, incidents of medication bias occurred less frequently in the intervention group. Self-efficacy scores for rationalized medication administration were significantly higher in the intervention group than in the control group. Involvement in medication safety behaviors was significantly higher in the intervention group than in the control group

Table 3 (continued)

First author and year of publication	Country	Type of intervention	Study population	Total sample size(cases) and dropout rate	Elements of intervention	Study setting	Data collection time	Outcome indicators (research tools)	Study results
Na Li [36] 2021	China	Quasi-experimental study	Older people with coronary heart disease	*N* = 70 (60) Intervention group = 35 (31) Control group = 35 (29) Dropout rate = 14.29%	**Intervention group:** interactive drug literacy intervention Intervention period: 12 weeks Intervention frequency: during hospitalization: 1 time per day, 30 ~ 40 min each time; home phase: 1 time per month, 20 min each time Intervention components: during hospitalization: 1-to-1 knowledge lectures, skills training, peer-to-peer exchanges; after discharge: online tutorials, follow-up visits, lectures and Q&A sessions **Control group:** routine care	Cardiology Department + WeChat	Preintervention At discharge At the end of the intervention At the end of 4th postintervention weekend	Involvement in medication safety behavior: Inpatient/Home Patient Involvement in Medication Safety Behavior Scale Medication bias: Medication Error Questionnaire Self-efficacy: SEAMS Health literacy: Coronary Heart Disease Related Knowledge Literacy Assessment Scale, Medication Skills Literacy Questionnaire Lipids, angina severity Readmission rate	An interactive drug literacy intervention increased patient involvement in medication safety behaviors, reduced medication errors, and improved health literacy and rational medication self-efficacy. It was effective in reducing patients' lipids and alleviating angina severity, but did not reduce readmission rates

Table 3 (continued)

First author and year of publication	Country	Type of intervention	Study population	Total sample size(cases) and dropout rate	Elements of intervention	Study setting	Data collection time	Outcome indicators (research tools)	Study results
Jiayi Mao [34] 2022	China	RCT	Older people with chronic diseases	*N* = 94 (89) Intervention group = 49 (46) Control group = 45 (43) Dropout rate = 5.32%	**Intervention Group:** Intelligent drug management system intervention Intervention period: 12 weeks Intervention frequency: full follow-up Tools: medication management system + WeChat applet + telephone follow-ups **Control group:** home visits by family doctors, regular follow-ups, educational activities on medication knowledge	Hospital + home	Preintervention At the end of the intervention	Involvement in medication safety behavior: MMAS-8 Health literacy: Medication Literacy Questionnaire Self-efficacy: SEAMS	After 3 months of intervention, the scores and differentials of involvement in medication safety behaviors and rational medication self-efficacy were higher in the intervention group than in the control group, and the number of delayed medication, missed medication, and incorrect medication instances were fewer than those in the control group; in the intervention group, whether or not participants used the WeChat applet did not have a statistically significant effect on the scores of medication knowledge and the differentials

PAM-13 Patient Activation Measure, *MMAS-8* Morisky Medication Adherence Scale-8, *SEAMS* Self-efficacy for Appropriate Medication Use Scale

study from America and four from China, published between 2010 and 2022, with a total of 388 participants. Of these, two were randomized controlled trials, whereas the remaining three were quasi-experimental studies. The types of chronic diseases studied included coronary heart disease [28, 36], diabetes mellitus [35], and mixed types of chronic diseases [28, 33–36]. The sample size ranged from 70 to 120, with dropout rates varying between 5.32% and 18.98% across the studies [28, 33–36]. In terms of intervention elements, the main patient engagement interventions to ensure medication safety included health education [28, 33–36], motivational interviewing [28], medication reconciliation [34]. Intervention formats include one-on-one interventions [28, 33–36], group interventions [33, 35], offline interventions [28], combined online and offline interventions [33, 35], and online interventions [36]. Patient engagement hardware and software platforms/tools included a WeChat platform [35, 36], an intelligent medication management system [36], the '5 Moments of Medication Safety' tool [35], a medication dispenser box [35], a reminder box [28], and a home involvement medication safety guidebook [28]. The durations for intervention/follow-up were predominantly 12 weeks [28, 34–36], although one study did not specify this information [33]. The intervention periods were hospital-home transition [34–36] and within-home/community settings [28, 33]. In terms of intervention frequency, hospitalization periods were 1–2 times per day [35], home periods were 1–2 weekly interventions [28] or 1 time per month [34, 35], one study supervised throughout [36], and one study was unknown [33]. The intervention duration was 10–15 min for telephone counseling [33], 20 min for online health education [35], 30–40 min for offline health education [35], 30–60 min for motivational interviews [28], 2 h for seminars [33], and unknown in one study [34]. Assessments were systematically conducted at defined time points, including at baseline [28, 33–36], at discharge [35], on day 7 postdischarge [34], at the end of the 1st month postdischarge [34], at the end of the 2nd month postdischarge [34], at the end of the intervention [28, 33–36], at the 4th postintervention weekend [28, 35], at the end of the 3rd month postintervention [28], and at the end of the 6th month postbaseline [33]. The outcome indicators included psychosocial (i.e., patient involvement in medication safety [34–36]/ positivity [28, 33]/ self-efficacy [28, 33–36]/ medication bias [28, 34, 35]/ health literacy [35, 36], etc.), disease-specific (i.e., blood glucose [34]/blood lipids [35]/angina severity [35], etc.), and health care utilization (i.e., readmission rates [35]) variables.

Discussion

This study systematically reviewed the effectiveness of interventions aimed at promoting older people's involvement in medication safety behaviors. The five studies included [28, 33–36] demonstrated that interventions such as health education, motivational interviewing, and medication reconciliation effectively enhanced older people's health literacy, medication engagement, and self-efficacy.

The findings revealed the diversity and complexity of interventions focused on "Patient involvement in medication safety." The effectiveness of interventions varied significantly across different settings. In hospitals, interventions were mainly delivered through face-to-face, individual or group formats [35, 36], focusing on medication decision-making and reconciliation [35]. This process involved comparing the patient's current medications with prescribed regimens to ensure consistency, adjusting inappropriate medications in collaboration with the healthcare team, and improving older people's sense of safety and involvement in medication management [37, 38]. This aligns with the findings of Beuscart JB [37].

In community or home settings, interventions were more focused on regular health education [28, 33] and motivational interviewing [28], equipping older people with skills in medication storage, handling expired drugs, and self-monitoring. These measures helped them adjust their medication lists and manage potential side effects [39, 40]. Health education not only increased patients' awareness of medication use but also encouraged their active involvement in medication safety behaviors, thus reducing medication errors [36, 41]. In this study, effective medication education formats included one-on-one interactive knowledge sessions [36], peer education [36], online lectures and Q&A [36], and telephone follow-ups [34–36]. Other studies have shown that feedback-based education can improve patient safety and foster shared decision-making [42, 43]. Motivational interviewing emphasized patient self-decision-making, strengthening doctor-patient cooperation and communication, thereby encouraging greater involvement in medication safety [28, 44].

During the transition from hospital to home, intervention formats became more diverse, with increasing use of hybrid online and offline approaches [35, 36] and even fully online methods [35]. Examples include the use of WeChat platforms [36] and intelligent medication management systems [34], which expanded the channels for patient involvement in medication safety and facilitated better information sharing between patients and healthcare providers. Current technologies also include mobile apps [45], smart pillboxes [46],

and Bluetooth wearable devices [47]. However, older people may resist or face barriers to adopting mobile health technologies due to low electronic health literacy, personal habits, or complex device interfaces [48], and the actual effectiveness of these interventions remains to be further validated. Moreover, differences in the tools used to assess patient involvement across studies could affect the comparability of results, highlighting the need for standardized tools to ensure consistency in research findings [49].

Patient involvement in medication safety is an active process of acquiring disease and medication information, empowering individuals to identify medication-related issues [50]. As involvement increases, positive changes occur in medication management behaviors [51], helping older people develop self-management and self-care abilities [52]. Sediling [53] demonstrated that hospitalized patients' involvement in medication safety management effectively prevented medication errors, improved adherence, and enhanced treatment outcomes. The studies by Niu Xiaodan [35] and Li Na [36] further emphasized the critical role of patient involvement in improving lipid profiles and managing blood glucose. However, most older people with chronic conditions have not fully recognized their role in health management [28]. Current clinical practice often prioritizes disease-specific treatment, neglecting a comprehensive assessment of the patient's overall health status [54], which increases medication risks for older people with multiple chronic conditions [55]. Therefore, it is crucial to position patients as the central subjects in health management, encouraging their active involvement in medication safety management. The theme of World Patient Safety Day 2022, "Medication Safety: Medication Without Harm," also underscored the global trend of empowering patients to take an active role in the medication process [56].

Despite the positive effects shown by these interventions, there remains a lack of detailed data regarding intervention frequency, duration, and the relative importance of different components. The included studies were of low quality, with considerable heterogeneity in intervention forms and content, and small sample sizes, limiting the generalizability and comparability of results. Therefore, more high-quality research is needed to verify the impact of these interventions on older people's involvement in medication safety behaviors. Future studies should also strive to standardize the evaluation tools for patient involvement and develop more tailored interventions based on the individualized needs of older people to ensure their effective participation in medication safety management.

Conclusion

It is crucial for older people to engage in medication safety behaviors. Analysis of the studies revealed that interventions for patient engagement in medication safety involved techniques such as interactive health education, motivational interviewing, and medication reconciliation. Unfortunately, there are few programs and participants that empower older people to engage in medication safety. There is a lack of direct evidence showing that these interventions can effectively improve medication safety behaviors in older people with chronic conditions. Therefore, more high-quality studies are needed to assess the true effects of these interventions and offer better support and guidance to older patients. Therefore, comprehensive studies on the motivational mechanisms and barriers to participation in medication safety among older people with chronic diseases are essential to effectively promote proper engagement in medication safety behaviors among older people, thereby enhancing patient health and safety.

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
MEDLINE	Medical Literature
PsycINFO	Psychology Informatics
CNKI	China National Knowledge Infrastructure
WanFang Data	China WanFang Data
VIP	China Science and Technology Journal Database
CBM	China Biology Medicine disc
OVID	Ovid Technologies
EMBASE	Excerpta Medica Database
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PROSPERO	Prospective Register of Systematic Reviews
EQUATOR	Enhancing the quality and transparency of health research
RCT	Randomized Controlled Trial
MINORS	Methodological Index for Nonrandomized Studies

Supplementary Information

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Additional file 1: Appendix 1. Search terms for the studies.

Additional file 2: Appendix 2. The intervention criteria examples.

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Authors' contributions

Ting Lin led the project and was responsible for the review and contributed substantially to the conception, design, drafting, and completion of the manuscript. Weixi Xu made a substantial contribution to the study conception and design, was involved in drafting the manuscript, literature searching, and screening, and contributed critically to important intellectual content. Xiaoyan Lin contributed to the design and acquisition of the data and the drafting of the manuscript. Huiqi Lai, Yaqin Ren and Hongjiang Ye contributed significantly to the design and acquisition of the data and participated in the

drafting of the manuscript. Ting Lin, Weixi Xu, Huiqi Lai, Yaqin Ren and Hongjiang Ye provided final approval for the final version of the manuscript, take full responsibility for the content of the manuscript and agree to be accountable for all aspects of the work, including its accuracy and integrity. All authors have read and approved the final manuscript.

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Data availability
Data supporting the results of this study are provided in the Supplementary Information document.

Declarations

Ethics approval and consent to participate
N/A.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

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