

Selection of interventions aimed at improving medication adherence in patients with multimorbidity

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ABSTRACT

Objectives To select interventions aimed at improving medication adherence in patients with multimorbidity by means of a standardised methodology.

Methods A modified Delphi methodology was used to reach consensus. Interventions that had demonstrated their efficacy in improving medication adherence in patients with multimorbidity or in similar populations were identified from a literature search of several databases (PubMed, EMBASE, the Cochrane Library, Center for Reviews and Dissemination, and Web of Science). 11 experts in medication adherence and/or chronic disease scored the selected interventions for appropriateness according to three criteria: strength of the evidence that supported each intervention, usefulness in patients with multimorbidity, and feasibility of implementation in clinical practice. The final set of interventions was selected according to appropriateness and agreement based on the Delphi methodology.

Results 566 articles were retrieved in the literature search. Nine systematic reviews were included. 33 interventions were initially selected for evaluation by the panellists. Consensus after two Delphi rounds was reached on 16 interventions. Five interventions were categorized as educational, six as behavioural and five were related to other aspects of interest.

Conclusions The interventions selected following a comprehensive and standardized methodology, could be used to improve medication adherence in patients with multimorbidity.

INTRODUCTION

Pharmacological treatment is a key component in managing chronic disease. Its effectiveness, to a great extent, depends on medication adherence,¹ defined as the extent to which a patient continues the agreed-upon mode of treatment under limited supervision.² Lack of adherence to chronic treatment is of great concern due to its high prevalence and its association with poor disease control, and increased morbidity, mortality and health expenditure.^{3,4}

Adherence rates vary greatly among different studies.⁵ Medication adherence is usually highest for short-term treatment and at the beginning of therapy. However, rates decrease with time, resulting in problems during long-term treatment.⁶ Lack of adherence is multifactorial in origin and related to the patient, their pharmacotherapy and the associated health professionals. Interventions need to be designed or adapted to improve medication adherence in accordance with the patient's characteristics.⁷

Much literature has been produced on the efficacy of different interventions aimed at improving medication adherence.⁸ Nevertheless, the exclusion of patients with multiple chronic conditions from clinical trials has been well documented and limits the external validity of clinical trials for these patients.⁹ Such trials may have included patients with multiple chronic conditions, but they are not identified clearly because interventions focus on a single condition, making the interventions of less interest to patients with multiple conditions. Consequently, numerous gaps remain in our knowledge concerning interventions to reduce non-adherence in patients with multimorbidity.

In the absence of consistent research evidence, expert consensus is a useful and appropriate resource. The Delphi method is recognised as useful in dealing with complex topics where clear evidence is lacking and the subjective judgements of experts could be of value.¹⁰ This method combines the best available scientific evidence with the collective judgement of experts to yield a statement regarding the appropriateness of performing a procedure.¹¹

The aim of this work is to select interventions aimed at improving medication adherence in patients with multimorbidity by means of a standardised methodology.

METHODS

The study was performed between September 2013 and December 2014, using a modified Delphi method.¹¹

In brief, the first step consists of identifying a list of clinical scenarios which are subsequently assessed individually and anonymously by an expert panel in two successive rounds. The experts' responses are processed to identify which aspects the group agrees on. In our case, the scenarios consisted of possible interventions aimed at improving medication adherence in patients with multimorbidity.

Literature review and development of scenarios

To identify the interventions, a literature search was performed without date restriction in the following databases (September 2013): PubMed, EMBASE, the Cochrane Library, Center for Reviews and Dissemination (CRD) and Web of Science (WoS).¹² The literature review was performed in accordance with the PRISMA statement.¹³ Articles were included if they assessed the efficacy of interventions to improve medication adherence in comparison with the usual clinical practice or other interventions. The study population had to be patients with multimorbidity, polymedicated



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patients or those with conditions usually present in patients with multimorbidity (conditions associated with end-organ damage or chronic conditions with high morbidity and/or mortality and/or the potential to become unstable).¹⁴ The search was restricted to systematic reviews of randomised clinical trials published in English or Spanish.

After removing duplicate articles, two independent reviewers assessed eligibility based on the title and abstract, reviewing the whole text if there was any doubt. In case of discrepancies between the two reviewers, a third researcher was consulted.

After the selection of studies, two reviewers independently extracted and tabulated outcome data using a pre-designed form, with an adjudicator resolving any disagreements. Extracted data included the characteristics of studied populations and the interventions that showed a statistically significant benefit in adherence rate. Both researchers assessed the risk of bias of systematic reviews included using the AMSTAR scale.¹⁵ This instrument comprises 11 concise criterion items. Each item is given a score of 1 if the specific criterion is met, or a score of 0 if the criterion is not met, is unclear or is not applicable. An overall score of review quality is then calculated: a score of 8–11 indicates high quality, 4–7 medium quality, and 0–3 low quality.

Finally, the selected interventions were grouped according to the Peterson *et al* classification which categorises interventions as educational or behavioural.¹⁶ The remaining interventions were included in a third group related to other aspects of interest. This list of interventions selected after the literature review was the basic working document used in the panel process.

Selection of expert panel

The panel of experts consisted of 11 members from five Spanish regions whose characteristics are shown in table 1 (see also Acknowledgements). The experts were recruited by telephone and email. They were informed about the aim of the study, the estimated workload and the schedule. A written agreement was requested from recruited panellists.

Expert panel evaluations

The experts participated in two consecutive rounds. For the first round, panellists received by mail, along with the rating forms, the following documents: the literature review, list of scenarios, definitions of terms, and instructions for rating. In addition, panellists were encouraged to add to this initial list of scenarios others based on their own experience.

Table 1 Characteristics of the expert panel (n=11)

Characteristics	n (%)
Sex	
Male	6 (54.5)
Female	5 (45.5)
Experience and knowledge profile	
Medication adherence	5 (45.5)
Chronic patients	5 (45.5)
Both	1 (9.0)
Profession	
Physician	6 (54.5)
Pharmacist	5 (45.5)
Work setting	
Hospital	7 (63.6)
Primary care	4 (36.4)

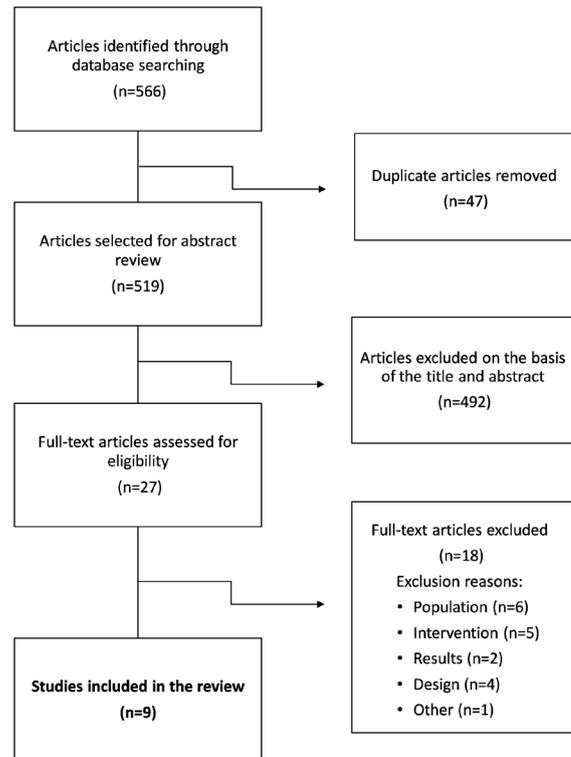


Figure 1 Flow diagram of the study selection process.

For every scenario, panellists were asked to rate the appropriateness from 1 to 9 (1 inappropriate; 9 appropriate) of the following three criteria: strength of the evidence that supported each intervention, usefulness in patients with multimorbidity, and feasibility of its application in clinical practice.

The results obtained were statistically analysed. The median and IQR were both calculated, as well as the level of agreement reached between panellists for each scenario. According to a modified Delphi method, each of the three criteria evaluated for each scenario (strength of the evidence, usefulness and feasibility) were classified as appropriate, inappropriate or uncertain. The operational definitions of levels of appropriateness are shown in the online supplementary material. The scenarios in which the three criteria were categorised as appropriate were selected.

In the second round, experts were asked to re-evaluate the appropriateness of the scenarios for which consensus had not been achieved in the first round. For each scenario they received the median and the IQR of all the experts' first-round ratings for each criterion, together with their own specific ratings. They were also provided with the comments and/or suggestions made anonymously during the first round by all the experts. Based on this information, experts could reconsider their scores from the first round. The results obtained from the second round were analysed and classified as in the first round.

RESULTS

Review of information and selection of indications

The literature review¹² included a total of 566 articles, from which nine systematic reviews were selected.^{17–24} Figure 1

Table 2 Characteristics of included systematic reviews

Article	Publication date	Number and design of included studies	Type of intervention	AMSTAR criteria
Kripalani <i>et al</i> ²⁰	2007	37 RCT	10 (27%) behavioural 12 (32%) educational 15 (41%) other	Medium quality
Haynes <i>et al</i> ¹⁸	2008	78 RCT	15 (19%) behavioural 11 (14%) educational 52 (67%) other	High quality
Williams <i>et al</i> ¹	2008	8 RCT	8 (100%) other	Medium quality
George <i>et al</i> ¹⁹	2008	8 RCT	8 (100%) other	Medium quality
Vervloet <i>et al</i> ²¹	2012	13 RCT	13 (100%) other	High quality
Viswanathan <i>et al</i> ¹⁷	2012	62 RCT	15 (24%) behavioural 3 (5%) educational 44 (71%) other	Medium quality
Moullec <i>et al</i> ²²	2012	18 RCT	1 (6%) behavioural 1 (6%) educational 16 (88%) other	Medium quality
Molloy <i>et al</i> ²³	2012	16 RCT	6 (38%) behavioural 10 (62%) other	Medium quality
Omran <i>et al</i> ²⁴	2012	8 RCT	2 (25%) behavioural 6 (75%) other	Medium quality

RCT, randomised clinical trial.

shows the flow diagram for the selection of articles. The main characteristics of the included systematic reviews are shown in [table 2](#). None of the systematic reviews selected were specifically focused on patients with multimorbidity but considered patients with multiple chronic conditions,^{1 17} polymedicated patients^{1 18 19} or patients with chronic conditions commonly associated with multimorbidity.^{1 17 18 20–24}

According to the AMSTAR scale,¹⁵ two reviews were rated as high quality^{18 21} and seven were categorised as moderate quality.^{1 17 19 20 22–24} The overall score of each systematic review ranged from 5 to 9 (out of 11) with a mean value of 6.2. The AMSTAR items with the highest compliance rate were: adequate description of the included studies (nine out of nine systematic reviews),^{1 17–24} comprehensive literature search (eight systematic reviews)^{1 17–22 24} and appropriate methodology to combine findings (seven systematic reviews).^{1 17 20–24} In contrast, a lower compliance rate was observed for the following items: conflict of interest statement (two systematic reviews)^{18 21} or likelihood of publication bias assessed (no systematic reviews).

Based on the literature review, 33 interventions aimed at improving adherence were identified. According to the Peterson *et al* classification,¹⁶ 10 interventions were categorised as educational and nine as behavioural. Fourteen interventions included other aspects of interest. These interventions were organised in 33 scenarios and included in the first Delphi survey.

Results of the evaluation rounds

[Figure 2](#) is a flowchart of the process used to identify the final interventions aimed at improving adherence in patients with multimorbidity. [Table 3](#) summarises the results obtained for each scenario in the two evaluation rounds.

The response rate among panellists was 100% for both rounds. In the first round, the panellists reached agreement on the three criteria evaluated for eight of the 33 interventions assessed. Three of the eight interventions were educational, three behavioural and two included other aspects of interest. As the rest were categorised as uncertain or inappropriate regarding at least one of the three criteria evaluated, they were re-evaluated

in the second round. Consensus was reached on eight additional interventions in the second round.

The final set included 16 interventions organised as follows: five educational interventions, six behavioural interventions and five interventions including other aspects of interest. [Table 4](#) shows the 16 interventions considered by consensus suitable for improving medication adherence in patients with multimorbidity.

DISCUSSION

Sixteen interventions aimed at improving medication adherence in patients with multimorbidity were identified using a standardised methodology. Five interventions were categorised as educational, six as behavioural and five included other aspects of interest.

To the best of our knowledge, this is the first study to use Delphi methodology to identify interventions aimed at improving medication adherence in patients with multimorbidity. The Delphi method has been used before to develop consensus-based solutions for medication adherence but focused on the general population.²⁵ Despite differences in terms of population between our study and that of Clyne *et al*,²⁵ both highlight the importance of improving patient education. According to Bosworth *et al*, interventions such as motivational interviewing, counselling and shared decision-making are required in order to make this change happen.²⁶

On the other hand, our results indicate that it is necessary improve both patient knowledge and caregiver education. These results are consistent with previous studies that demonstrated the importance of caregivers in improving medication adherence in patients with chronic conditions.²⁷

Regimen complexity has been associated with adverse drug events, non-adherence and hospital readmission. More recently, medication regimen complexity has also been identified as an overall predictor of all-cause mortality.²⁸ Consequently, behavioural interventions aimed at reducing and managing medication complexity should be highlighted.

According to the panellists, enhancing communication between the patient and health professionals is another

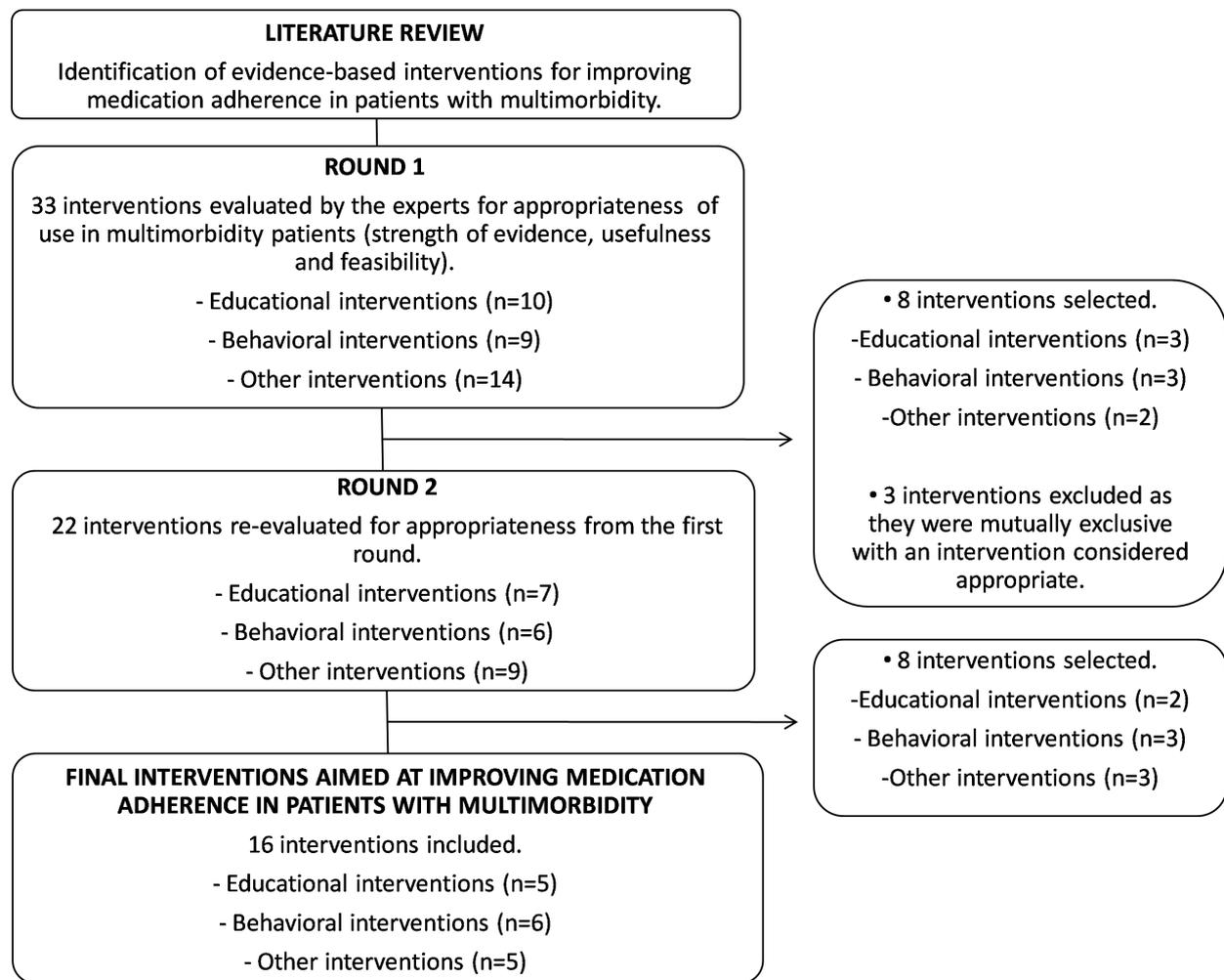


Figure 2 Flow diagram for the process used to identify the interventions aimed at improving adherence in patients with multimorbidity.

behavioural approach that should be adopted. A similar conclusion was reached in other studies.²⁹

Either way, due to the lack of adherence observed in long-term treatment,⁶ our results show that an initial intervention should be followed by a reinforcement intervention. Another key point is that interventions to support medication adherence may be multi-faceted, as also pointed out by other studies.^{7 8 25}

Other research⁸ in this area describes complex adherence interventions which are difficult to put into practice. However, our study only includes interventions judged feasible to implement in clinical practice. In addition, as there are discrepancies in the Delphi literature for establishing consensus, more stringent criteria have been adopted in order to select the most useful interventions. In this way, only interventions in which the three criteria evaluated (evidence, usefulness and feasibility) were categorised as appropriate were selected.

There are several limitations to the current study. The Delphi method is a rigorous technique very suitable for achieving consensus in areas of uncertainty. It is quite frequently used for topics, such as medication adherence, where multiple stakeholder groups are potentially involved.¹¹ However, like most research techniques, the Delphi method also has disadvantages.¹⁰ In modified Delphi designs, the initial list of scenarios is based on a review of the relevant literature and so may be limited by the researcher. However, our panel members were asked to add other scenarios to the initial list. Bias may also occur depending

on how the questions are formulated or who is invited to participate in the panel.

This study does not indicate how to combine interventions for the best result or if one intervention is more effective than another. However, the list of selected interventions should be customizable according to the objectives and the resources at each specific setting or institution.

Although patients with multimorbidity are strictly characterised by Bernabeu *et al*,¹⁴ the lack of a MeSH term for multimorbidity is another limitation. For this reason, we used broad search terms. To ensure that no potentially eligible papers were missed, the authors involved in the review were experts in the discipline of multimorbidity (JG-B, MDN-M, MCP-G, MO-B).

Finally, a multidisciplinary expert panel was recruited in an effort to reflect different views. However, patients or caregivers were not included on the panel. In addition, all panellists were from Spain, so the final list of interventions may not adequately reflect the full range of situations.

Once the interventions aimed at improving adherence in patients with multimorbidity have been selected, it is necessary to demonstrate their effectiveness. Therefore, future research could include a randomised clinical trial examining the efficacy of the selected interventions for promoting adherence in the studied population.

Medication adherence is a key element in achieving therapeutic goals in patients with chronic conditions,³⁰ especially

Table 3 Summary of the results obtained for the scenarios evaluated in the two evaluation rounds

Scenarios	Interventions	Appropriateness*						
		Round 1			Round 2			
		Strength of evidence	Usefulness	Feasibility	Strength of evidence	Usefulness	Feasibility	
Educational interventions	1	Individual sessions with the patient and the main caregiver	U	A	A	A	A	A
	2	Group sessions with patients with the same primary condition	U	U	I	U	A	I
	3	A pharmacist holds educational sessions	U	A	U	U	A	U
	4	A physician, pharmacist or nurse holds educational sessions†	A	A	A	–	–	–
	5	Other relatives besides the main caregiver attend educational sessions	U	A	A	U	A	A
	6	Information about the importance of medication adherence to achieve the desired therapeutic goals is given to the patient and the main caregiver‡	A	A	A	–	–	–
	7	Information about the therapeutic indication of every prescribed drug is given to the patient and the main caregiver‡	A	A	A	–	–	–
	8	Information about potential medication-related problems as well as instructions for their prevention and/or detection is given to the patient and the main caregiver	U	A	U	A	A	A
	9	The duration of educational sessions is less than 30 min	U	A	U	U	A	A
	10	The duration of educational sessions is from 30 to 60 min	U	U	I	U	U	I
Behavioural interventions	11	Strategies to simplify the regimen‡	A	A	A	–	–	–
	12	Strategies for tailoring treatment to the patient's lifestyle‡	A	A	A	–	–	–
	13	Delivery of personalised dosage systems‡	A	A	A	–	–	–
	14	Self-reported adherence using a medication chart to check off administered doses	U	U	U	U	A	U
	15	Medication chart providing valuable information about patient pharmacotherapy	U	A	A	A	A	A
	16	Providing the patient or main caregiver with a way to communicate with a health professional (reactive contact)	U	A	U	A	A	A
	17	Providing the health professional with a way to communicate with the patient or main caregiver (proactive contact)	U	A	U	A	A	A
	18	Use of smartphone medication adherence apps	U	A	U	U	A	U
	19	Use of electronic reminders	U	A	U	U	A	U
Other interventions	20	Educational interventions exclusively	U	U	A	U	U	A
	21	Behavioural interventions exclusively	U	U	U	U	U	U
	22	Combined educational and behavioural interventions	A	A	U	A	A	A
	23	Interventions systematically applied in the same way in all patients	U	U	A	U	A	A
	24	Interventions adapted to each patient's needs according to medication adherence barriers‡	A	A	A	–	–	–
	25	Interventions applied exclusively on hospital discharge‡	U	U	A	–	–	–
	26	An initial intervention at hospital discharge followed by a reinforcement intervention‡	A	A	A	–	–	–
	27	Reinforcement intervention performed in person or by telephone.	U	A	A	A	A	A
	28	The reinforcement intervention is performed in person§	U	A	U	–	–	–
	29	The reinforcement intervention is performed by telephone§	U	A	A	–	–	–
	30	The reinforcement intervention is performed no later than 3 months after hospital discharge	U	A	A	U	A	A
	31	The reinforcement intervention is performed between 3 and 6 months after hospital discharge	U	U	A	U	A	A
	32	The reinforcement intervention is performed simultaneously with a medical consultation regardless of the time elapsed since hospital discharge	U	A	A	A	A	A
	33	The smartphone adherence apps are developed by non-profit entities¶	U	A	U	A	A	A

*A, appropriate; I, inappropriate; U, uncertain.

†Scenarios not re-evaluated in the second round because they were considered appropriate by consensus in the first round.

‡Excluded after the first round as indication 26 was considered appropriate and they are mutually exclusive.

§Excluded after the first round as indication 27 was considered appropriate and they are mutually exclusive.

¶Excluded after the second round as the use of electronic devices was not considered appropriate (indications 18 and 19).

Table 4 Interventions aimed at improving medication adherence in patients with multimorbidity

Interventions	
Educational interventions	<ul style="list-style-type: none"> - Individual sessions with the patient and the main caregiver - A physician, pharmacist or nurse holds educational sessions - Information about the importance of medication adherence to achieve the desired therapeutic goals is given to the patient and the main caregiver - Information about the therapeutic indication of every prescribed drug is given to the patient and the main caregiver - Information about potential medication-related problems as well as instructions for their prevention and/or detection is given to the patient and the main caregiver
Behavioural interventions	<ul style="list-style-type: none"> - Strategies to simplify the regimen - Strategies for tailoring treatment to the patient's lifestyle - Delivery of personalised dosage systems - Medication chart providing valuable information about patient pharmacotherapy - Providing the patient or main caregiver with a way to communicate with a health professional (reactive contact) - Providing the health professional with a way to communicate with the patient or main caregiver (proactive contact)
Other interventions	<ul style="list-style-type: none"> - Combined educational and behavioural interventions - Interventions adapted to each patient's needs according to medication adherence barriers - An initial intervention at hospital discharge followed by a reinforcement intervention - The reinforcement intervention is performed in person or by telephone - The reinforcement intervention is performed simultaneously with a medical consultation regardless of the time elapsed since hospital discharge.

those with multimorbidity, due to their greater vulnerability. The interventions in this work selected using a comprehensive and standardised methodology could be an effective way for improving medication adherence in this type of patient.

Key messages

What is already known on this subject

- ▶ Medication adherence is a key element in achieving therapeutic goals in patients with multimorbidity.
- ▶ There are numerous gaps in our knowledge concerning interventions to reduce non-adherence in patients with multimorbidity due to their exclusion from clinical trials.
- ▶ The Delphi technique is well suited as a method for consensus-building when literature evidence is lacking.

What this study adds

- ▶ The study identifies appropriate interventions for improving medication adherence in patients with multimorbidity using a comprehensive and standardised methodology.
- ▶ The selected interventions were those whose evidence, usefulness and feasibility were categorised as appropriate.
- ▶ Any intervention to support medication adherence may be multi-faceted and include both educational and behavioural aspects.

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Contributors Conception or design of the work: JG-B, MDN-M, MO-B, BS-R. Data collection: JG-B, EC-C. Data analysis and interpretation: JG-B, MDN-M, MCP-G, MO-B. Drafting the article: JG-B, EC-C, BS-R. Critical revision of the article: all authors. Final approval of the version to be published: all authors.

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