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Developing a list of high-alert medications for patients with chronic diseases

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ABSTRACT

Background: Patients with chronic diseases often receive multiple medications and are associated with increased vulnerability to medication errors. Identifying high-alert medications for them would help to prioritize the interventions with greatest impact for improving medication safety. The aim of this study was to develop a list of high-alert medications for patients with chronic illnesses (HAMC list) that would prove useful to the Spanish National Health Service strategies on chronicity.

Methods: The RAND/UCLA appropriateness method was used. Drug classes/drugs candidates to be included on the HAMC list were identified from a literature search in MedLine, bulletins issued by patient safety organizations, incidents recorded in Spanish incident reporting systems, and previous lists. Eighteen experts in patient/medication safety or in chronic diseases scored candidate drugs for appropriateness according to three criteria (evidence, benefit and feasibility of implementing safety practices). Additionally they rated their priority of inclusion on a Likert scale.

Results: The final HAMC list includes 14 drug classes (oral anticoagulants, narrow therapeutic range antiepileptics, antiplatelets – including aspirin –, antipsychotics, β-blockers, benzodiazepines and analogues, corticosteroids long-term use, oral cytostatics, oral hypoglycemic drugs, immunosuppressants, insulins, loop diuretics, nonsteroidal anti-inflammatory drugs, and opioid analgesics), and 4 drugs or pairs of drugs (amiodarone/ dronedarone, digoxin, oral methotrexate and spironolactone/eplerenone).

Conclusions: An initial list of high-alert medications for patients with chronic diseases has been developed, which can be built into the medication management strategies for chronicity to guide the implementation of efficient safety strategies and to identify those patients at greater risk for preventable adverse drug events.

1. Introduction

The concept of "high-alert or high-risk medications", referring to those medications that bear a heightened risk of causing significant patient harm when used in error, is well-recognized in the area of patient safety. This concept was introduced by the Institute for Safe Medication Practices (ISMP) after conducting a study in 161 American hospitals which revealed that a relatively small number of medications was responsible for the majority of medication errors resulting in serious consequences for patients [1]. Based on these findings, error reports submitted to the ISMP's voluntary medication error reporting program (MERP), and on expert opinions, the ISMP established a list of high-alert medications for acute care settings, which has been periodically updated [2,3], and recommended that institutions implement risk-reduction strategies focused on the use of these drugs. Reducing harm from high-alert medications has been a priority of the programs and recommendations developed by leading organizations such as the Joint Commission, the Institute for Health Improvement, the National Patient Safety Agency and the National Quality Forum [4–7].

Caring for people with chronic diseases has become a huge challenge for healthcare systems worldwide. To address the phenomena of chronicity, new organizational models of healthcare delivery have emerged to respond to the needs of chronic patients and the healthcare burden that they generate, focused on integrated, coordinated, efficient, and patient centered care [8–10]. In Spain, the Ministry of Health has elaborated the "*Strategy for Addressing Chronicity in the National Health Service*" that includes among its main objectives the stratification and targeting of the population according to different levels of risk and need for care, enabling the design of specific, effective, efficient and evidence-based interventions for each subgroup of patients [11]. It also emphasizes the need to optimize the use and management of medications in order to improve health outcomes and reduce adverse drug events, especially

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in patients with multiple chronic conditions, since they often receive numerous medications and have complex medication regimens.

These issues led us to consider that medication management strategies for chronicity would benefit from incorporating the concept of high-alert medications, since this would help to prioritize the interventions that have the greatest impact on medication safety, and to optimize resources. It would also provide a tool that would enable professionals to identify patients who are at the greatest risk of experiencing harm when medication errors occur, and for whom proactive interventions could significantly improve medication safety.

However, as far as we know, there is no list of high-alert medications specifically designed for patients with chronic diseases. The list that comes closest to this context is a brief list of high-alert medications for ambulatory healthcare settings that was compiled by the ISMP in the United States in 2008, within the framework of research to identify high-alert medications dispensed from community pharmacies [12]. For this reason, we designed this project with the objective of developing a list of high-alert medications, specifically designed for patients with chronic illnesses (HAMC list), that would be useful to the Spanish National Health Service.

2. Methods

The HAMC list was developed between September, 2013, and March, 2014, using the RAND/UCLA appropriateness method [13]. This method combines the synthesis of the scientific evidence with the opinions of experts.

2.1. Information search and development of scenarios

The first step in the RAND/UCLA method consists of identifying a list of indications or scenarios, which are subsequently assessed by an expert panel in two successive rounds. In our case, the scenarios consisted of the medication candidates for being considered high-risk medications for chronic patients and therefore included on the HAMC list. To identify these drugs, a literature review on MedLine (1/1/2003 to 10/31/2013) was conducted to search for publications about preventable adverse drug events or medication errors with harm in the ambulatory setting, or that had led to emergency room visits, or hospitalization, because many interventions aimed at managing chronic diseases are delivered in the primary care setting. The search was restricted by language (English and Spanish) and population (adults only) (see search strategy in online supplementary Appendix A). Publications meeting the following criteria were selected: a) gathered information about incidents derived from the clinical use of medications, b) differentiated preventable adverse events or provided sufficient information to make a reasonable determination, and c) reported the number or percentage of incidents associated with each different drug class/drugs or provided sufficient information to make the calculation.

The above information was completed with grey literature by searching on the web pages of several safety organizations for bulletins and alerts referring to serious medication errors. Not included in this search were ISMP-Spain bulletins that are published based on errors notified to the reporting system which were reviewed as indicated below.

In addition, the databases of the Spanish ISMP-Spain and SiNASP incident reporting systems were examined to gather reports of errors with harm caused by medications used in the treatment of chronic patients. Finally, the lists of high-alert medications published by the ISMP for hospitals and ambulatory settings were reviewed, and drug classes/drugs used in treating chronic diseases were selected.

2.2. Selection of the panel of experts

The criteria considered when selecting the experts were: a balanced ratio of men to women and of experts in patient/medication safety and in chronic patients; representation from primary care, hospital, and administration; representation from specialists in internal medicine, geriatrics, family medicine, hospital pharmacy, community pharmacy, primary care pharmacy, and nursing; and representation from different autonomous regions in Spain. The group of experts consisted of 18 members whose characteristics are shown in Table 1 (see Acknowledgements).

2.3. Expert panel evaluations

The experts participated in two consecutive rounds. In the first round, they received the following documents by email: a questionnaire with the scenarios as a list of the drug classes or individual drugs to be evaluated for inclusion on the HAMC list, tables synthesizing the evidence for each scenario, definitions of terms, and instructions for rating. They were asked to assess the appropriateness of the drug classes or individual drugs to be considered as high-risk medications in chronic patients (not whether these drugs are or are not inappropriate to be prescribed or used in chronic older patients). Each scenario with the drug class or individual drug was rated for appropriateness for inclusion on the HAMC list according to the following three criteria: strength of evidence supporting that this drug class or individual drug has a heightened risk of causing significant patient harm when used in error, benefits to be obtained in chronic patients from the implementation of safe practices with thus drug, and feasibility of implementing safe practices. Following the RAND/UCLA method, these criteria were rated on a scale of 1 to 9 points, from “completely inappropriate” to “completely

Table 1
Characteristics of the experts on the panel (n = 18).

Characteristics	Participants	
	n	%
Gender		
-Men	10	55.6
-Women	8	44.4
Experience and knowledge profile		
-Medication/patient safety	6	33.3
-Chronic diseases	6	33.3
-Both	6	33.3
Profession		
-Physician	7	38.9
-Pharmacist	8	44.4
-Nurse	3	16.7
Work setting		
-Hospital	7	38.9
-Primary care	6	33.3
-Nursing homes	2	11.1
-Administration	3	16.7
Specialization		
-Internal medicine	2	11.1
-Geriatrics	1	5.6
-Family medicine	4	22.2
-Hospital pharmacy	4	22.2
-Primary care pharmacy	2	11.1
-Community pharmacy	2	11.1
-Nursing	3	16.7
Spanish autonomous region		
-Andalucía	3	16.7
-Aragón	1	5.6
-Asturias	1	5.6
-Canarias	1	5.6
-Cantabria	1	5.6
-Castilla-La Mancha	1	5.6
-Cataluña	2	11.1
-Extremadura	1	5.6
-Galicia	1	5.6
-Madrid	4	22.2
-Navarra	1	5.6
-País Vasco	1	5.6

appropriate", respectively. Also included on the questionnaire was an additional section for evaluating the priority for inclusion of each dug class or individual drug on the HAMC list, using a Likert scale from 1 to 5, from "low priority" to "maximum priority", respectively.

The results obtained were analyzed statistically. The median and interquartile range were both calculated, as well as the level of agreement reached for the criteria for each scenario. Appropriateness was classified following the RAND-UCLA method into three levels: appropriate, inappropriate and uncertain. With respect to inclusion priority, the principal measures of central tendency and dispersion for the ratings assigned to each scenario by the panelists were calculated. Finally, the scenarios in which the three criteria were categorized as appropriate were tentatively admitted. Scenarios were eliminated in this first round if considered inappropriate according to one of the three criteria, if judged uncertain according to some or all the criteria and rated with a lower priority for inclusion (median ≤ 2.5) or if they included drug classes or drugs that could overlap with other scenarios (i.e. opioids and morphine or fentanyl) and received a lower rating.

The second evaluation round consisted of a face-to-face meeting during which the results of the first round were presented. The experts were asked to re-evaluate the appropriateness of the scenarios for which consensus had not been achieved in the first round and consequently had not been eliminated, and to re-rate the inclusion priority for some drug classes or drugs. Each panel member received an individualized evaluation questionnaire with the scenarios that needed to be re-evaluated which showed the median and interquartile range of all the experts' first round ratings for each criterion, together with his own specific ratings. Also provided were the corresponding inclusion priority results. During the meeting, the moderator introduced the areas with greatest discrepancy, and, afterwards, the experts discussed each area and re-evaluated the scenarios individually and anonymously. Additionally, the experts had the option of changing or adding new scenarios to those established in the first round.

The results obtained from this second round were analyzed and classified using the same methods as with the first round. Finally, a drug class or drug was included on the HAMC list when the experts judged it appropriate for inclusion, according to the three criteria evaluated, and its inclusion priority had a median of ≥ 4 and a P25 ≥ 3.

3. Results

3.1. Review of information and definition of scenarios

The literature review yielded a total of 701 articles, of which 94 were initially selected based on the title and abstract screening. After reviewing the full text of the articles, only 19 were finally selected [14–32]. The main reasons for exclusion are summarized in Fig. 1.

From the grey literature review, 44 safety bulletins and alerts referring to drug classes/drugs used in chronic diseases and associated with serious errors were retrieved [33–76]. Database searches in the ISMP-Spain and the SiNASP reporting systems allowed for the identification of 36 scenarios. Finally, from the high-alert medications list published by the ISMP for hospitals and for ambulatory settings [3,12], 6 drug classes and 1 drug, and 7 drug classes and 6 drugs were selected, respectively, some of which coincide.

Using the information above, 66 scenarios corresponding to 48 drug classes and 18 drugs were defined as candidates for inclusion on the HAMC list. Available evidence for each scenario was gathered onto tables which showed the source of the information and the types of errors most frequently reported (see online supplementary Appendix B).

3.2. Results of the evaluation rounds

Fig. 2 shows a scheme of the process used to elaborate the HAMC list and Table 2 summarizes the results obtained for each scenario in the evaluation rounds.

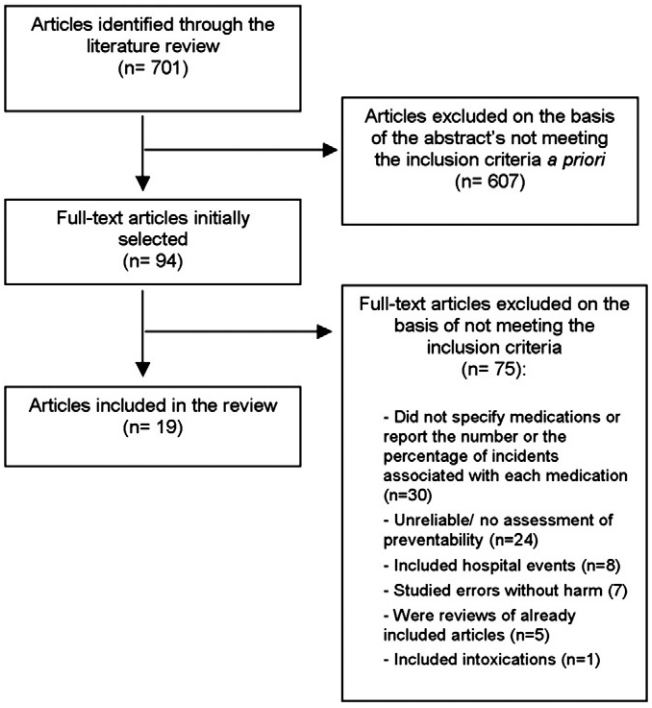

Fig. 1. Flow diagram of the selection of articles on preventable adverse events of medications used in patients with chronic diseases.

After the results of the first round were analyzed, 12 scenarios, agreed upon by all the experts, were provisionally admitted to the list, 25 scenarios were selected for re-evaluation in the second round, and 29 scenarios were eliminated. Of the latter, 3 scenarios were eliminated because of having been found inappropriate for inclusion according to at least one criterion (thyroid therapy, propylthiouracil, and colchicine), 14 for being categorized as uncertain for all criteria and rated with a low priority for inclusion (i.e. anticholinergics, quinolones, cotrimoxazole), and 12 because they included medications that overlapped with others and had received lower scores.

In the second round, experts met face-to-face to re-evaluate a total of 25 scenarios. They also discussed the criteria that drugs should meet for inclusion on the HAMC list. These criteria were: having the potential to cause severe harm to patients when used in error or having been identified as one of the drugs most commonly associated with preventable adverse events responsible for hospital admissions, being used in chronic treatments (not in acute, short term treatments), and not being prescribed and dispensed exclusively in hospitals.

Of the 25 scenarios, 19 were re-evaluated for appropriateness for inclusion on the HAMC list because results in the first round had been uncertain for at least one of the criteria (i.e. low molecular weight heparins, benzodiazepines and analogues, antiepileptic drugs, anti-infective drugs, antiretroviral drugs, immunosuppressants) or for all criteria (i.e. thiazide diuretics, potassium sparing diuretics, calcium channel antagonists, nitrates, corticosteroids, antidepressants). In addition, 6 scenarios classified as appropriate were rerated for inclusion priority, because they were related to earlier scenarios and it was decided that all should be discussed together and rerated again (i.e. renin–angiotensin system antagonists along with calcium channel antagonists and other cardiovascular classes, benzodiazepines with benzodiazepines and analogous).

During the meeting, the panelists proposed 5 new scenarios in order to broaden, specify, or better profile some of the scenarios from the first round. Thus, they suggested evaluating amiodarone/dronedarone (broadening the amiodarone scenario), and specifying spironolactone/eplerenone (instead of potassium sparing diuretics), diltiazem/verapamil

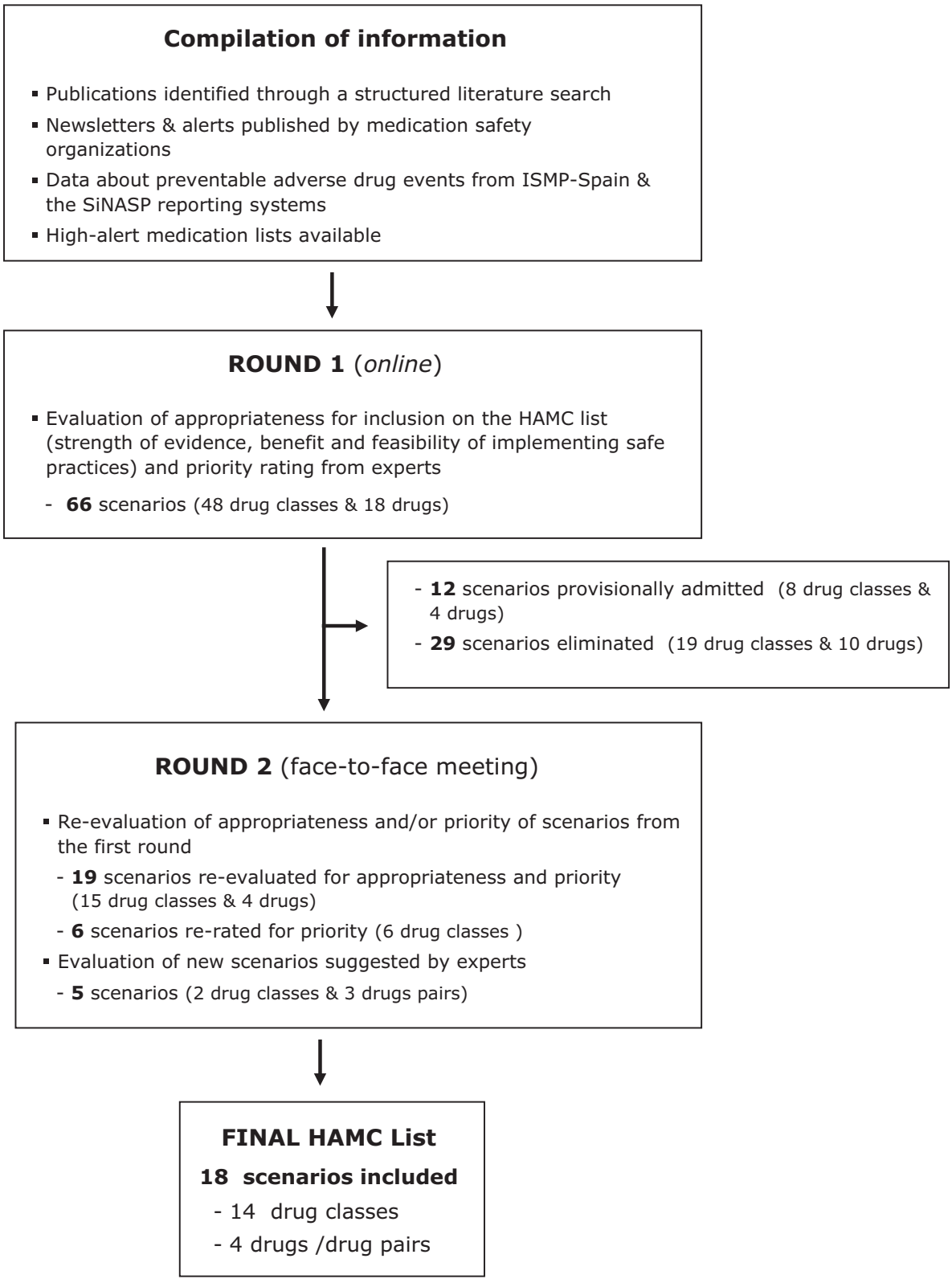

Fig. 2. Flow diagram for the process used to elaborate the list of high-alert medications for patients with chronic diseases.

(instead of all calcium channel antagonists), long-term corticosteroids ≥3 months (instead of corticosteroids) and narrow therapeutic range antiepileptic drugs, including the 3 antiepileptic drugs previously evaluated individually but not other new agents (instead of antiepileptic drugs).

Of the 19 scenarios that were re-evaluated for appropriateness for inclusion, only 2 were finally classified as appropriate (benzodiazepines and analogous and immunosuppressants), while for the other 17 scenarios consensus was not reached. Three of the 5 new scenarios were judged appropriate and were added to the HAMC list: spironolactone/

Table 2
Summary of the results obtained for the scenarios evaluated in the two evaluation rounds.

Scenario	Drug classes/drugs	Round 1 result[a]	Final result [b]
Section 1. Cardiovascular drugs			
1	Cardiovascular agents	Eliminated AP	Excluded
2	Diuretics	Re-evaluate P	Excluded O
3	Loop diuretics	Re-evaluate P	Included
4	Thiazide diuretics	Re-evaluate AP	Excluded
5	Potassium sparing diuretics	Re-evaluate AP	Excluded
6	Drugs affecting renin–angiotensin system	Re-evaluate P	Excluded P
7	Antiadrenergic agents	Re-evaluate AP	Excluded
8	β-Adrenergic blockers	Re-evaluate P	Included
9	Calcium antagonists	Re-evaluate AP	Excluded
10	Digoxin	Admitted T	Included
11	Nitrates	Re-evaluate AP	Excluded
12	Amiodarone	Admitted T	Excluded O
13	Statins/lipid-lowering drugs	Eliminated AP	Excluded
N1	Spironolactone/eplerenone	–	Included
N2	Verapamil/diltiazem	–	Excluded
N3	Amiodarone/dronedarone	–	Included
Section 2. Hemostasis and coagulation			
14	Anticoagulants -all-	Eliminated O	Excluded
15	Anticoagulants, oral	Admitted T	Included
16	Warfarin/acenocoumarol	Eliminated O	Excluded
17	Heparins and other injectable anticoagulants	Re-evaluate P	Excluded P
18	Low molecular weight heparins	Re-evaluate AP	Excluded
19	Antiplatelets (including aspirin)	Admitted T	Included
Section 3. Hormones and metabolism			
20	Insulin + oral hypoglycemics	Eliminated O	Excluded
21	Insulins	Admitted T	Included
22	Oral hypoglycemic drugs	Admitted T	Included
23	Metformin	Eliminated O	Excluded
24	Corticosteroids	Re-evaluate AP	Excluded
25	Thyroid therapy	Eliminated I	Excluded
26	Propylthiouracil	Eliminated I	Excluded
N4	Corticosteroids long-term use (≥3 months)	–	Included
Section 4. Anti-inflammatory, analgesics–antipyretic and antigout drugs			
27	Nonsteroidal anti-inflammatory drugs	Admitted T	Included
28	COX-2 inhibitors	Eliminated AP	Excluded
29	Non-opioid analgesics	Eliminated AP	Excluded
30	Antigout drugs	Eliminated AP	Excluded
31	Colchicine	Eliminated I	Excluded
Section 5. CNS drugs			
32	Opioid analgesics	Admitted T	Included
33	Morphine	Eliminated O	Excluded
34	Fentanyl patches	Eliminated O	Excluded
35	Oxycodone	Eliminated O	Excluded
36	Hydromorphone	Eliminated O	Excluded
37	Methadone	Eliminated O	Excluded
38	Antiepileptics	Re-evaluate AP	Excluded
39	Carbamazepine	Re-evaluate AP	Excluded
40	Phenytoin	Re-evaluate AP	Excluded
41	Valproic acid	Re-evaluate AP	Excluded
42	Antiparkinsonian drugs	Eliminated AP	Excluded
43	Antipsychotics	Admitted T	Included
44	Typical antipsychotics	Eliminated O	Excluded
45	Atypical antipsychotics	Eliminated O	Excluded
46	Lithium	Admitted T	Excluded P
47	Bezodiazepines and analogues	Re-evaluate AP	Included
48	Benzodiazepines	Re-evaluate P	Excluded O
49	Benzodiazepines (intermediate-acting)	Eliminated O	Excluded
50	Antidepressants	Re-evaluate AP	Excluded
51	Tricyclic antidepressants	Re-evaluate AP	Excluded
52	SSRI antidepressants	Re-evaluate AP	Excluded
53	Antidepressants except SSRI and tricyclic	Eliminated AP	Excluded
N5	Antiepileptics (narrow therapeutic range)	–	Included
Section 6. Antiinfective drugs			
54	Antiretroviral drugs	Re-evaluate AP	Excluded
55	Antiinfective drugs	Re-evaluate AP	Excluded
56	Cotrimoxazole	Eliminated AP	Excluded
57	Fluoroquinolones	Eliminated AP	Excluded
Section 7. Cytostatics and immunosuppressants			
58	Cytostatic drugs, oral	Admitted T	Included
59	Methotrexate, oral (non-oncologic use)	Admitted T	Included
60	Immunosuppressants	Re-evaluate AP	Included
61	Tacrolimus	Re-evaluate AP	Excluded
Section 8. Other			
62	Pregnancy category X drugs	Eliminated AP	Excluded
63	Respiratory therapy drugs	Eliminated AP	Excluded
64	Inhaled and oral bronchodilators	Eliminated AP	Excluded
65	Inhaled corticosteroids	Eliminated AP	Excluded
66	Anticholinergics	Eliminated AP	Excluded

[a] Round 1 result: Admitted T = Tentatively admitted; Re-evaluate AP = Re-evaluate appropriateness and rerate priority; Re-evaluate P = Rerate Priority; Eliminated O = Eliminated due to overlapping; Eliminated I = Eliminated for inappropriateness; Eliminated AP = Eliminated for uncertainty and low priority.
[b] Final result: Included; Excluded; Excluded O = Excluded for overlapping; Excluded P = Excluded based on priority.

eplerenone, long-term corticosteroids (≥3 months) and narrow therapeutic range antiepileptic drugs.

On the other hand, of the 6 scenarios for which inclusion priority was evaluated, 2 were definitively excluded from the list (renin–angiotensin system antagonists and heparins and other parenteral anticoagulants), 2 more were excluded because other similar drug classes (diuretics and benzodiazepines) surpassed them in the priority rating, while 2 were definitively included (loop diuretics and β-adrenergic blockers).

3.3. High-alert medication final list

Table 3 shows the final HAMC list along with the final scores assigned to the medications after the second round for appropriateness and priority for inclusion. The definitive list includes a total of 18 scenarios: 14 classes of drugs and 4 drugs or pairs of drugs.

4. Discussion

The term "high-alert medications" emerged from the necessity of defining target medications on which to concentrate efforts and prioritize interventions in order to improve medication safety. Considering that only approximately 1 to 5% of medication errors result in harm [77], implementing interventions centered only on the specific drugs most often implicated in errors resulting in harm may be a more efficient approach. This concept and the first list of high-alert medications were created in hospital settings where the first epidemiologic studies on adverse events related to healthcare were carried out and safety programs were consequently first implemented [78,79]. However, healthcare systems have recently focused on the care of chronic patients, adopting new models to emphasize the integration, coordination and continuity of care across all healthcare settings [8–10]. For this

Table 3
Scores after the second evaluation round for appropriateness and priority for inclusion for the drug classes/drugs on the HAMC list[a].

High-alert drug classes/drugs for patients with chronic diseases	Appropriateness for inclusion on the HAMC list[b]			Inclusion priority[c]		
	Strength of the evidence	Benefit from implementing safe practices	Feasibility of implementing safe practices			
	Median (IQR)	Median (IQR)	Median (IQR)	Median	P25	Mean
►*Therapeutic classes*						
Anticoagulants, oral	8 (7.25–9)	8 (7–9)	8 (7–8.75)	5	5	4.8
Antiepileptics (narrow therapeutic range)	7 (6–8)	7 (5–8)	7 (6–8)	4	3	3.5
Antiplatelets (including aspirin)	7.5 (7–9)	7 (7–8.5)	7 (5.25–8.75)	4	3	3.8
Antipsychotics	8 (6–8.75)	8 (6.25–8)	7 (6–7.75)	4	3	3.8
β-Adrenergic blockers	8 (7–8.75)	7.5 (6–9)	7 (6–8.75)	4	3	3.7
Benzodiazepines and analogues	7 (6.25–8.75)	7.5 (6.25–8.75)	7 (6–7)	4	4	4.3
Corticosteroids long-term use (≥3 months)	8 (7–8)	8 (7–8)	7 (6–7)	4	3	3.7
Cytostatic drugs, oral	8 (7–8)	7 (6.25–9)	7 (7–8)	4	3.25	4
Immunosuppressants	7 (6–7)	7 (6–9)	7 (6–8)	4	3	3.7
Insulins	8 (7.25–9)	8.5 (7.25–9)	7.5 (7–8)	5	4.25	4.7
Loop diuretics	8 (6.25–8.75)	8 (6.25–8.75)	7 (6–8)	4	4	4.1
Nonsteroidal anti-inflammatory drugs	8.5 (8–9)	7.5 (7–9)	7 (6–8)	4.5	3	4.1
Oral hypoglycemic drugs	8 (8–9)	8 (8–9)	7 (7–7.5)	5	4	4.3
Opioid analgesics	9 (8–9)	8 (7.25–9)	7.5 (7–8)	5	5	4.7
►*Specific medications*						
Amiodarone/dronedarone	7 (5–7)	7 (6.5–8)	7 (5–8)	4	4	4.2
Digoxin	8 (7.25–9)	8 (8–9)	8 (8–9)	5	4	4.5
Methotrexate, oral (non-oncologic use)	8 (6–8)	8 (6.25–9)	7.5 (5.25–8.75)	4	3.25	3.9
Spironolactone/eplerenone	7 (6–7)	7 (5.75–7.25)	7 (6–7.25)	4	3	3.9

IQR: interquartile range. P25: 25 percentile.
[a] Drug classes/drugs included: all those that were judged appropriate for inclusion on the HAMC list after the second round (for the 3 criteria of evidence, benefit from and feasibility of implementing safe practices) and that had a median for priority inclusion ≥4 and a P25 ≥ 3.
[b] Appropriateness scale: 1 = completely inappropriate to 9 = completely appropriate.
[c] Priority scale: 1 = low priority to 5 = high priority.

reason, this study aims to optimize medication therapy for chronic patients by developing a list of high-alert medications specifically for them.

The HAMC list was developed following a procedure similar to that used to create the ISMP lists. These lists were generated from information about serious medication errors gathered from epidemiological studies, reporting systems and expert opinions [3,12]. The methodology used was the RAND-UCLA, and was based on information collected through studies on preventable adverse events that had led to hospitalization or emergency room visits (since these served as indicators of the most serious errors resulting from medication use in the primary care setting), as well as from other studies, bulletins, published alerts, and incidents collected from the ISMP-Spain and SiNASP, in conjunction with the opinions of experts in the fields of safety and chronic patients.

Only 6 medication classes and 1 individual medication coincide with the high-alert medication lists previously published [3,12]. Some medications on ISMP's current lists received the highest priority for inclusion on the HAMC list, such as oral anticoagulants, opioids, insulins and oral hypoglycemic, which are medications with a high risk of causing harm when errors occur and are used to treat chronic diseases. These drug classes are included as priority targets in the patient safety strategies promoted by different organizations and healthcare authorities [5,6]. Oral cytostatic drugs, oral methotrexate for non-oncologic use, and immunosuppressants, present on one or both ISMP high-alert lists, were also incorporated onto the HAMC list.

The experts decided that heparins and other injectable anticoagulants, included on the ISMP lists, had a lower priority for inclusion, since they are generally used in short-term treatment after patient discharge. Antiretroviral drugs were not included because in Spain they are prescribed and dispensed exclusively in hospitals and, as mentioned earlier, the panelists agreed to include only medications that may also be prescribed and dispensed in the ambulatory setting.

The HAMC list adds new medications that were not included on the available high-alert lists. Nonsteroidal anti-inflammatory drugs, antiplatelets, β-blockers, oral digoxin, and antipsychotic drugs, were included because they are frequently involved in errors related to incorrect prescription or inconsistent monitoring leading to hospital admissions [17,80,81]. For the same reason, the list includes loop diuretics (often prescribed in high doses and related to adverse events associated with inadequate follow-up) as well as potassium sparing diuretics, spironolactone and eplerenone, associated with hyperkalemia as a consequence of inadequate potassium monitoring, high doses and/or simultaneous use with drugs affecting the renin–angiotensin system.

Benzodiazepines and analogous drugs, such as zolpidem, that are extensively used in Spain [82], were also included and, even though they do not have a narrow therapeutic range, they have been associated with numerous errors related to long treatment duration, duplicative therapy, and inappropriate prescribing. The experts were concerned about the incorrect use of these medications because of the repercussions in chronic patients, being associated with an increased risk of falls and hip fractures, road traffic accidents, cognitive impairment, dementia, and even an increase in mortality [83].

Drugs associated with harm during long-term treatment, obviously common in chronic diseases, also emerged as high risk medications. In this sense, the panelists proposed defining the scenario of "long-term use corticosteroids", which was included by consensus, instead of just "corticosteroids", a scenario that they had not considered as appropriate in the first round, because short-courses of steroid therapy less frequently lead to high risk situations.

The fact that antimicrobial medications are normally used for acute treatment was the principal reason they were excluded from the HAMC list. However, experts did recognize the problems caused by the overuse of these drugs in Spain, and the need to strength programs developed at the national level in order to optimize their use and reduce antimicrobial resistance [84,85]. Another drug class that was not included on the HAMC list comprises those medications that interfere with the renin–angiotensin system, even though the available evidence shows that they are associated with a high percentage of adverse events that

lead to hospitalization, because the experts felt that their use was extremely frequent use in chronic patients and assigned them low priority for inclusion.

Several limitations derived from the methodology used should be mentioned. First of all, we must point out that the RAND/UCLA technique, though it presents characteristics that are apparently objective, is really a subjective method, since it basically measures opinions [86]. However, this technique has advantages over other methods also used to reach for reaching consensus, because it allows for both confidential ratings as well as group discussion, and it has shown good reproducibility. In fact, it is considered as a rigorous method to be used where a combination of scientific evidence and expert opinion is required, and it is recommended when determining appropriateness of a procedure or developing decision-making tools [87]. Secondly, it must be remembered that the results will always depend on the composition of the panel. The aim of this project was to bring together the views of front-line chronic care practitioners as well as experts on patient/medication safety. The latter, more knowledgeable about the concept of high-alert medications, may have shown a tendency to produce a restrictive list, based fundamentally on narrow therapeutic range medications, while the experts in chronicity would tend to broaden the list, incorporating medications considered inappropriate for older patients [88,89]. Still, a high degree of consensus was obtained for the medications finally included on the list and, in any case, the list created is a work in progress that will need to be updated periodically.

The HAMC list can be a useful tool for developing and prioritizing the implementation of medication safety strategies for chronic patients. These strategies should cover all the stages of the medication use process, from prescribing to dispensing, administering, monitoring, and educating patients and caregivers, and should be established for each particular drug, taking into consideration the most frequent types of errors and the characteristics of its use in chronic patients. Risk-reduction strategies should include decision support systems integrated with electronic prescribing, with alerts about maximum doses and drug interactions, and reminders about appropriate duration of treatment or laboratory monitoring, as well as the establishment of programs for regular medication review and for comprehensive medication reconciliation at care transitions. Particular attention should be given to providing education specific to each drug for patients and caregivers that includes precautions that should be taken to avoid repetition of errors previously detected with other patients.

In conclusion, an initial list of high-alert medications for patients with chronic diseases was developed by an expert panel, and includes 14 drug classes and 4 drugs or pairs of drugs. The main contribution of this study is making available this initial reference list which can be built into the medication management strategies for chronicity to guide the implementation of medication error prevention activities focused on these drugs and to identify those patients at greater risk for preventable adverse drug events. As far as we know, this study is the first attempt to elaborate a high-alert medication list for chronic patients. Although generated to be used in Spain, this list could also be helpful for other countries, as a first step towards incorporating the concept of high-alert medications into chronicity strategies. However, more studies are needed to prove the effectiveness of this list in reducing medication adverse events.

5. Learning points

- A focus on “high alert medications” is a well-recognized approach in the area of patient safety.
- The study has identified 14 drug classes and 4 drugs or pairs of drugs to elaborate an initial list of high-alert medications for patients with chronic diseases. These drug classes/drugs have the potential to cause severe harm to patients when used in error (e.g. insulins, oral methotrexate) and/or are frequently associated with preventable adverse events responsible for hospital admission (e.g., nonsteroidal anti-inflammatory drugs, antiplatelets).
- This list may be used as a starting point for developing efficient strategies for reducing medication errors in chronic patients and for identifying those patients for whom proactive interventions could significantly improve medication safety.
- Being knowledgeable of this list may also contribute to optimizing medication management by healthcare professionals and to improving educational interventions directed towards patients and caregivers.

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Competing interests

The authors declare that they have no competing interests.

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