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ORIGINAL ARTICLE

Quality of interaction database management systems

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KEY WORDS
Drug interaction;
Database management systems;
Quality assurance

Abstract
Objective: To identify drug interaction databases (DID) and assess the quality of their structures.
Method: A search was made of the literature for DID and a series of exclusion and structural quality criteria were defined (at least 4 quality criteria: classification according to severity, classification according to level of evidence, bibliographical reference data, description of clinical management, and 11 criteria used for weighting). The level of compliance of every DID with the criteria defined was analysed, together with the level of compliance of each criteria in each DID.
Results: A total of 54 DID were identified, 30 of which complied with exclusion criteria and 15 of which did not meet the minimum criteria. The rest of the criteria were evaluated in 9 DID: Bot-plus and Medinteract (100%), SEFH Guide, Lexi-interact and Medscape (89%), Hansten (83%), Micromedex and Stockley (78%), Drug Interactions Facts (68%). Ninety-two percent of the DID describe the mechanism of action, 87% classify the information according to the active ingredient, 75% do not state they have any conflict of interest, classify according to level of severity, have electronic format, and are easy to search. A total of 67% are specific DID, 62% are classified according to level of evidence, contain bibliographical references, and describe clinical management.
Conclusions: A third of the DID comply with the minimum criteria. Differences were observed in the level and compliance criteria among Spanish and foreign DID. Some of the main DID used as references in the bibliography have significant structural defects: no web presentation, no multi-check function and others.

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PALABRAS CLAVE
Interacciones medicamentosas;
Bases de datos;
Evaluación de calidad

Calidad estructural de las bases de datos de interacciones

Resumen
Objetivo: Identificar bases de datos de interacciones medicamentosas (BDIM) y valorar su calidad estructural.
Método: Se realizó una búsqueda bibliográfica de BDIM y una definición de criterios de exclusión y calidad estructural (4 criterios de calidad mínima: estratificación según grado de gravedad, clasificación según nivel de evidencia, referencia bibliográfica de datos, descripción del manejo clínico, y 11 criterios que aportaban peso ponderal). Se analizó el grado de cumplimiento en cada BDIM de los criterios definidos y el grado de cumplimiento de cada criterio en todas las BDIM.
Resultados: Se identificaron 54 BDIM de las que 30 cumplían criterios de exclusión y 15 no reunían criterios mínimos. Se valoró el resto de los criterios en 9 BSM: Bot-plus y Medinteract (100%), Guía de la SEFH, Lexi-interact y Medscape (89%), Hansten (83%), Micromedex y Stockley (78%), Drug Interactions Facts (68%). El 92% de las BDIM describen mecanismo de acción, el 87% estructura la información por principio activo, el 75% no declara tener conflicto de intereses, estratifica según grado de gravedad, tiene soporte informático y la búsqueda es ágil. El 67% son BDIM específicas, el 62% clasifica según nivel de evidencia, contiene referencias bibliográficas y describe el manejo clínico.
Conclusiones: Un tercio de las BDIM cumplen criterios mínimos. Se encontraron diferencias en el grado y el criterio de cumplimiento entre las BDIM españolas y las de otros países. Algunas de las principales BDIM utilizadas como referentes en la bibliografía presentan importantes deficiencias estructurales: la falta de presentación web y de función multi-check y otras.

Introduction

Interactions between medications administered to a patient contribute to concomitant morbi-mortality and, in many cases, could be preventable. A study carried out in Denmark upon 26 337 patients with at least 2 prescribed medications detected 21 293 different combinations, of which 4.4% carried a risk of producing a severe interaction. In this same study, 1.2% of hospitalisations were related to medicinal interactions.[1]

In Spain, the APEAS study[2] found that 47.8% of adverse events detected in the primary health care field were due to medications, of which 3.5% were a consequence of medicinal interaction. Another published study reveals that 9.9% of the population over 65 years of age is at risk of clinically significant interactions. The study notes that there is an exponential growth in the risk of interactions being produced with a higher number of medications.[4,6] Polymedication could therefore present a risk of interaction. In Australia 14% of the general population uses more than 4 medications, and in the population over 75 years of age this figure increases to 40%. Data from the UK indicates that 30% of the population over 75 years takes more than 4 medicines. In Spain, a study carried out in a rural area with basic health care indicated that 11.37% of the population was over 65, with an ageing population of 65% and an average prescription rate of 4 medications, and a greater number of prescribed medicines tallying with increased age.[7]

However, management of medicinal interactions in clinical consultation is not easy. The introduction of new technologies in primary health care and hospitals has brought a development in the form of computerised clinical history, which has opened up the possibility of incorporating decision support systems (DSS) with regard to interactions, which alert the user at the moment of prescribing medicines and report on possible courses of action. However, the introduction of these systems is not yet widespread. According to an investigation carried out in Spain in 2007, computer-assisted prescription is in place in only 22.4% of hospitals.[8] In primary health care, the development of electronic prescription has not apparently been accompanied (thus far) by tools for the clinical management of interactions. However, many have incorporated complete databases in consultation format, in order that the clinic may utilise them at their discretion and in specific cases.

In the absence of a DSS, any clinic that wishes to carry out a systematic follow-up of medicinal interactions must manage by itself the data sources and their assigned clinical relevance, ie, the influence which the data will have upon any modification of the therapeutic plan. And it is here where the range in databases and sources of information regarding interaction is such that it usually becomes impossible to manage physically. Furthermore, in a study carried out on just 5 databases,[9] it was found that the quality was very unevenly spread and the concordance was scarce, making it difficult to pinpoint real clinical importance in each of the interactions.[10]

The objective of this study is to assess the structural quality of various drug interaction databases (DID) in order to be able to subsequently create a decision support system.

Method

Search for databases

In order to identify existing interaction databases, a bibliographic search and exploration of grey literature was carried out. The bibliographic search was performed on MEDLINE using the following key words: "drug," "database*," and "interaction*." Subsequently, all the bibliographic citations found in the works obtained were reviewed. The search of grey literature was carried out using general information Internet search engines, using the following search terms: "drug," "database*," and "interaction."

Databases detailing interactions with no clinical practice, interactions with food, medicinal plants, or other products, results in languages other than English, French, or Spanish, results contained in systems covering very small localised areas, results containing information regarding only one group of medications, interactions concerning new drugs still in development or drugs which are not readily available for purchase or prescription, and medicines designed for the PDA since they compile their information from more general DIDs.

For the databases included in the study which were not freely available, an access licence was obtained or the relevant book or CD was purchased, as appropriate.

Definition and weighting of evaluation criteria

Given that it was not possible to locate suitable references, the researchers themselves established the evaluation criteria. The criteria used were diverse:

- Descriptive criteria: date of first edition, price, language, and number of interactions described. These factors were not used for quality evaluation
- Criteria used for evaluation (Table 1). Two types of criteria were used in turn: *a)* minimum quality criteria, ie, any database which does not meet these criteria is discarded for later evaluation (4 criteria), and *b)* criteria which add weighting to the evaluation (12 criteria). The latter, in turn, were divided into 2 groups according to the relative importance assigned by the research group: 7 criteria with a weighting of 10.76% (which in total counted as 75% of the evaluation) and 4 criteria with a weighting of 6.25% (making up 25% of the total evaluation)

Each criterion was assigned a score, as detailed in Table 1. Only those DIDs which met the minimum criteria were selected for the subsequent phase of the study, which consisted of assessing whether the remaining criteria were met, and assigning a score to the general level of fulfilment.

Two types of analysis were performed: *a)* for each DID the degree of compliance with the structural quality criteria was determined, and *b)* for each structural quality criterion the degree of compliance in different databases. This last analysis was carried out on all the selected DIDs and for the resulting division strata according to language or compliance with the minimum criteria.

Results

A total of 54 databases were identified, 37 from citations in articles found on MEDLINE and 18 from informal searches. Twenty-four of these databases fulfilled the inclusion criteria. Those databases which were excluded are detailed in Appendix 1,[42-82] no Spanish DID was excluded.

Of the selected DIDs, 6 were edited in Spain, 14 in the United States, 3 in the United Kingdom, and 1 in France. Among the Spanish databases, 1 was recovered from MEDLINE and the remaining 5 from grey literature.

Nine DIDs met the minimum quality criteria (Table 2), whereas 15 did not and, therefore, the remaining quality criteria were not applied to these. Table 3[28-41] summarises the characteristics of these unevaluated DIDs. Among the databases which did not fulfil the minimum criteria, 3 did not meet any of the 4 criteria, 2 failed to meet 3 criteria, 5 did not meet 2 criteria, and 5 failed to meet just 1 criterion.

With regard to structural quality, the values obtained for the different DIDs which exceeded the minimum criteria were: Bot-plus[11] and Medinteract[12] (100%), *Guía de la SEFH*,[13] Lexi-interact[14] and Medscape[15] (89%), Hansten[16] (83%), Micromedex[17] and Stockley[18] (78%), and Drug Interaction Facts[19] (67%).

Table 4 summarises the degree of compliance with each criteria for all of the analysed DIDs. The stratification of the degree of severity is the most common criterion overall. The Spanish DIDs have more of a tendency to include a description of severity, bibliographical reference, and description of clinical management, whereas the DIDs of other countries more frequently include classification of the level of evidence.

Discussion

A large number of databases concerning medicinal interactions exist internationally. More than half are inaccessible or of no clinical interest. Of the 24 selected databases, only 17 were in English and, therefore, the selection can be considered as global in character. The discovery of such a high number of databases concerning medicinal interactions apparently makes clear that, firstly, this is a high-interest area of pharmacotherapy and, secondly, there appears to be no defined international standard.[20]

Six databases were available in Spanish, of which 3 met the minimum quality requirements. Although not global in character, these can be considered a reference for the vast Latin American territories. Given that the majority of these were recovered from the grey literature, it is logical to assume that there should be a similar pattern in other languages; in other words, there are databases in any given language which are not referred to in scientific articles and, therefore, they are difficult for researchers of other languages to find.[21]

Along with the issue of language, the question of which drugs are included is also pertinent, not just due to their quantity but also their relevance. In other words, those DIDs which include all medications from a specific market (eg, Bot-Plus or Medinteract, which include all medicines

Table 1 Quality criteria used in the study. Definition, weighting, and allocation of points for each criterion

Criterion	Definition	Weighting	Score
Minimum criteria			
Stratification of degree of severity	Degree of severity defined?	Minimum criteria	Not scoreable
Classification according to level of evidence	Is there an evaluation of level of evidence?	Minimum criteria	Not scoreable
Bibliographical reference	Bibliographical references citation complete?	Minimum criteria	Not scoreable
Description of clinical management	Therapeutic approach proposed?	Minimum criteria	Not scoreable
Criteria weighted at 75%			
Authors	Who maintains the DID?	10.72%	1: academy, public administration, scientific society; 0: others
Declaration of no conflict of interest	Is the declaration made?	10.72%	1: yes/0: no
Last update update performed?	In which year was the most recent	10.72%	1: 2005-2006; 0: earlier
Periodicity of updates	With what periodicity have the last 2 updates been carried out?	10.72%	1: yes; 0: no
DID specificity	Is the DID specific to interactions, or is it part of a more general database?	10.72%	1: yes; 0: no
Multicheck structure	Is it possible to compare more than two active principles at once?	10.72%	1: yes; 0: no
Definition of action mechanism	Is the action mechanism of the interaction described?	10.72%	1: yes; 0: no
Criteria weighted at 25%			
DID structure	Is the search carried out using TG or AP, as opposed to trade name?	6.25%	1: if TG or SP; 0: trade name
Specificity of the interaction	Is the specific interaction of the AP defined, as opposed to the interactions of TGs?	6.25%	1: computer; 0: print
DID support	What type of support does the DID use? (CD, online, book, etc)	6.25%	1: computer; 0: print
Search speed	Are the results displayed quickly? (subjective criteria by the evaluator)	6.25%	1: yes; 0: no

AP indicates active principle; DID, drug interaction database; TG, therapeutic group.

registered in Spain), can be of more use in that particular market compared with other databases which may have more medicines listed yet exclude some which are commercialised in that country.

It is surprising that only 9 of the 24 DIDs selected complied with the required minimum quality criteria. Among those which did not comply are some of those DIDs most used as a reference for works in the field of drug interaction detection, both in primary health care environments and hospitals. The Spanish databases (both included and excluded) fulfil more of the minimum criteria than others; their weakest point is classification according to level of evidence. The non-Spanish databases place more emphasis on the stratification of degree of severity.

Among the 9 DIDs which met the minimum criteria, the heterogeneity in the classification format of these criteria should be highlighted.

Severity is classified into 2, 3, and even 4 levels, and neither the description or the underlying concept tally in virtually any of the databases. This presents a serious problem for the standardisation of this important issue. Particularly noteworthy is the fact that some DIDs do not stratify the degree of severity (Medical Letter, the most significant due to its widespread dissemination).

The same thing occurs with the classification of level of evidence. In some DIDs reference is made to the type of article supported, whereas in others a classification is made by the authors, in general not referring to the levels of

Table 2 General results for comparison of DIDs which met the minimum criteria and scores for the subsequent comparison criteria

	Bot-Plus, evaluation		Medinteract.net, evaluation		Lasefh Guide, evaluation		Lexi-interact, evaluation	
Stratification of degree of severity	Yes		Yes		Yes		Yes	
Interaction classification according to level of evidence	Yes		Yes		Yes		Yes	
Bibliographical reference to data origins	Yes		Yes		Yes		Yes	
Description of clinical management/recommended action when faced with an interaction	Yes		Yes		Yes		Yes	
Authors	General council of official colleges of pharmaceuticals	1	University of Barcelona	1	Spanish Society of Hospital Pharmacy	1	Lexi-comp, sector professionals and experts	0
Declaration of conflict of interests	No	1	No	1	Sí	0	No	1
Date of first edition					2000		Completed in 2006	
Last update	2006	1	Continuous update	1	2005	1	Immediate updates	1
Periodicity of updates	3 months	1	Continuous update	1	1 year	1	Immediate updates	1
Database specific to interactions	Yes	1	Yes	1	Yes	1	Yes	1
Multicheck	Yes	1	Yes	1	Yes	1	Yes	1
Mechanism/effect/ description	Yes	1	Yes	1	Yes	1	Yes, summary	1
Database structure (therapeutic groups, active principle, trade name, etc)	Searches for both active principle / speciality	1	Active principle/ trade name	1	Active principle	1	Active principle	1
Is a distinction made between interactions of the active principle and those of the group?	Yes	1	Yes	1	Yes	1	Yes	1
Database support (CD-ROM, book, online, etc)	CD-ROM	1	*On line*	1	CD-ROM	1	CD-ROM/*Online*	1
Good search speed	Yes	1	Yes	1	Yes	1	Yes	1
Availability	CD-ROM		www.medinteract.net		CD-ROM		www.lexi.com	
Price	Free to registered professionals		5-day trial (free). Six month trial (€20). One year trial (€30)		Free of charge		$1500	
Language	Spanish		Spanish		Spanish		English	
Number of interactions describeds	Medications registered in Spain		Medications registered in Spain		Medications registered in Spain		1800 active principles	
Final score	100%		100%		89.2%		89.2%	

Medscape, evaluation		Hansten, evaluation		Micromedex, evaluation		Stockley, evaluation		Drug Interaction Facts, evaluation	
Yes		Yes		Yes		Yes		Yes	
Yes		Yes		Yes		Yes		Yes	
Yes		Yes		Yes		Yes		Yes	
Yes		Yes		Yes		Yes		Yes	
Medical speciality	0	University of Washington, Seattle	1	Thomson Corporation	0	I.H. Stockley, University of Nottingham Medical School	1	Specialists in medicine and health	0
No	1	No	1	No	1	No	1	No	1
		50 years ago		1974		20 years ago. First Spanish edition 2004		Over 60 years ago	
2007	1	2007	1	2006	1	2006	1	2007	1
Immediate updates	1	Every 3 months	1		0	2 years	0		0
Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
Yes (up to 20)	1	No, by pairs	0	Yes	1	No, by pairs	0	Not describede	0
Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
Active principle	1	Active principle	1	Ability to search both by active principle and trade name	1	Organised into medicine group chapters, which are internally organised into active principle pairs	1	Active principle	1
Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
Online	1	Book	0	*Online*	1	*Book/online*	1	Book/CD-ROM	1
Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
www.medscape.com		Book		www.sefh.es		www.imedicinas.com		Book	
Free of charge		€59.60		€900		€300		Book $89.95, CD-ROM $235	
English		English		English		Spanish		English	
850 active principless				More than 8000		More than 2800 monographs		20 000 active principles	
89.2%		83.03%		78.5%		78.5%		67.85%	

Table 3 Comparison of drug interaction databases which did not meet the minimum quality criteria

	AGEMED,[28] evaluation	American Hospital Formulary Service Drug Information,[29] evaluationn	Drugdigest.org,[30] evaluation	Drugint,[31] evaluation	Drugs.com,[32] evaluation	Epocrates,[33] evaluation
Stratification of degree of severity	No	No	Yes	Yes	Yes	Yes
Interaction classification according to level of evidencea	No	No	Yes	No	Yes	No
Bibliographical reference to data origins	No	No	No	Yes	No	Yes
Description of clinical management/ recommended action when faced with an interaction	Yes	No	No	Yes	Yes	No
Authors	Spanish Drugs Agency	American Society of Health-System Pharmacists	Expert Group	Company created by 2 pharmaceu-ticals	Expert committee	Private company of experts
Declaration of conflict of interests	No	No	No	No		No
Date of 1st edition		1959				1998
Last update		2007	2004	2007	2006	2006
Periodicity of updates				4 months		
Database specific to interactions	No	No	Yes	Yes	Yes	Yes
Multicheck	No	Yes	Yes		Yes	Yes
Detailed description/effect/ action mechanism	Yes	Yes	Yes	Yes	Yes	Yes
Database structure (therapeutic groups, active principle, trade name, etc)	Active principle	Active principle	Active principle	Active principle	Active principle	Active principle
Is a distinction made between interactions of the active principle and those of the group?	Yes		No	Yes	No	No
Database support (CD-ROM, book, online, etc)	*Online*	Book	*Online*	*Online*	*Online*	*Online*
Good search speed	No		Yes	Yes	No	Yes
Availability	www.agemed.es	www.asph.org	www.drugdigest.org	www. drugmastersl. com	www.drugs. com	www.epocrates. com
Price	Free of charge	$239	Free of charge	6960 pesetas	Free of charge	Free of charge
Language	Spanish	English	English	Spanish	English	English
Number of interactions described	Commercialised mediciness	40 000 monographs	11 500 potential interactionss	2500	24 000 active principles	More than 3000 active principles

Guide to therapeutic prescription,[34] evaluation	Martindale, evaluation	Medicinet.com,[35] evaluation	MEDLINE.plus,[36] evaluation	Dr Koop,[37] evaluation	Rx-List.com, evaluation	Stokley reducido,[39] evaluation	The Medical Letter,[40] evaluation	Thesaurus des Interactions Medicamenteus,[41] evaluation
Yes	Yes	No	No	Yes	Yes	Yes	No	No
No	Yes	No	No	Yes	No	Yes	Yes	No
Yes	Yes	No	No	No	Yes	No	Yes	Yes
No	No	No	No	No	No	Yes	Yes	Yes
Coordinators of the Spanish Agency for Medicines and Healthcare Productss	Royal Pharmaceutical Society of Great Britain	MedicinNet, INC., expert group	Us National Library of Medicine and the National Institutes of Health	Company created by Dr Koop and specialist group	Experts	Stockley (reduced version)	Founded by Arthur Kallet and Dr Harrold Aaron. Expert ensemble	Agencia Française de Securité Sanitaire des Produits de Santé
	No	No	No	No	No	Yes	No	No
Part of the 51st edition of the British National Formulary	More than one century	1996					1982	
			2006	2007	2006		No. 3, in 2006	
	Updates every 3 years	Immediate	6 months				6 months	
No	No	No	No	No	No	Yes	Yes	Yes
Yes	Yes	No	No	No	No	No, by pairs	Yes (up to 9 active principles	No, by pairs
Yes	Yes	No	No, only the interaction is named	Yes	Yes	Yes	Yes	Yes
Active principle	Organised into drug groupss	Active principle	Active principle	Trade name	Ability to search both by active principle and trade name	Active principle	Active principle	Active principle
No	No	No	No	No	Yes	Yes	Yes	No
Online	Online	Online	Online	Online	Online	Online, CD-ROM	Online, CD-ROM	Online
No	Yes	Yes	Yes	No	Yes	Yes	Yes	No
www.imedicinas.com/GTPage/	www.imedicinas.com	www.medicinenet.com	www.medlineplus.gov	www.drkoop.com	www.fdb.rxlist.com	imedicinas.com	http://medletter.com	www.agmed.sante.gouv.fr
Free of charge	€550	Free of charge	Free of charge	$89, 1 year	Free of charge	€180	$89, 1 year (online)	Free of charge
Spanish	Spanish	English	Spanish	English	English	Spanish	English	French
Included in Appendix 1	More than 95 000 worldwide	2500 active principles	1000 medicines		Common monographs	More than 40 000	3000	Most active principless

Table 4 Drug interaction databases (DIDs) which meet each criterion

Criterion	Spanish (n=6)	Foreign (n=18)	Included (n=9)	Excluded (n=15)	All (n=24)
Descriptive criteria					
Language					
English	0	17 (64.44%)	6 (66.66%)	11 (73.33%)	17 (70.83%)
Spanish	6 (100%)	0	3 (33.33%)	3 (20%)	6 (25%)
French	0	1 (5.55%)	0	1 (6.66%)	1 (4.16%)
Number of interactions					
Described	6 (100%)	16 (88.88%)	8 (88.88%)	14 (93.33%)	22 (91.66%)
Unspecified	0	2 (11.11%)	1 (11.11%)	1 (6.66%)	2 (8.33%)
Date of 1st edition					
After 2000	1 (16.6%)	1 (5.55%)	2 (22.22%)	0	2 (8.33%)
Before 2000	1 (16.6%)	9 (50%)	3 (33.33%)	6 (40%)	10 (41.66%)
Unspecified	4 (66.6 %)	8 (44.44%)	4 (44.44%)	9 (60%)	12 (50%)
Price					
Free of charge	4 (66.6%)	8 (44.44%)	3 (33.33%)	9 (60%)	12 (50%)
Payment	2 (33.3%)	10 (55.5%)	6 (66.66%)	6 (40%)	12 (50%)
Minimum criteria					
Stratification of degree of severity	5 (83.3%)	13 (72.2%)	9 (100%)	9 (60%)	18 (75%)
Classification according to level of evidence	3 (50%)	12 (66.6%)	9 (100%)	6 (40%)	15 (62.5%)
Bibliographical reference	5 (83.3%)	10 (55.5%)	9 (100%)	6 (40%)	15 (62.5%)
Description of clinical management	5 (83.3 %)	10 (55.5%)	9 (100%)	6 (40%)	15 (62.5%)
All minimum criteria	3 (50%)	6 (33.3%)	9 (100%)	0	9 (37.5%9)
Weighted criteria					
Database specific to interactions	4 (66.6%)	12 (66.6%)	9 (100%)	7 (46.66%)	16 (66.66%)
Authors					
Scientific society	4 (66.6%)	12 (22.22%)	2 (22.22%)	6 (40%)	8 (33.33%)
University	1 (16.6%)	3 (16.6%)	3 (33.33%)	1 (6.66%)	4 (16.66%)
Private company	1 (16.6%)	11 (61.11%)	4 (44.44%)	8 (53.33%)	12 (50%)
Declaration of no conflict of interests	4 (66.6%)	16 (88.88%)	8 (88.88%)	12 (80%)	20 (83.3%)
Description of action mechanism	6 (100%)	16 (88.88%)	9 (100%)	13 (86.66%)	22 (91.66%)
Last update					
2005-2006	4 (66.6%)	14 (77.77%)	9 (100%)	9 (60%)	18 (75%)
Previous	0	1 (5.55%)	0	1 (6.66%)	1 (4.16%)
Unspecified	2 (33.3%)	3 (16.66%)	0	5 (33.33%)	5 (20.83%)
Periodicity of updates					
Less than 1 year	4 (66.6%)	6 (33.33%)	6 (66.66%)	4 (26.66%)	10 (41.66%)
More than 1 year	0	2 (11.11%)	1 (11.11%)	1 (6.66%)	2 (8.33%)
Unspecified	2 (33.3%)	10 (55.55%)	2 (22.22%)	10 (66.66%)	12 (50%)
Database structure					
Active principle	6 (100%)	16 (88.88%)	9 (100%)	13 (86.66%)	22 (91.66%)
Treatment Group	0	1 (5.55%)	0	1 (6.66%)	1 (4.16%)
Trade name	0	1 (5.55%)	0	1 (6.66%)	1 (4.16%)
Multicheck	4 (66.6%)	9 (50%)	6 (66.66%)	7 (46.66%)	13 (54.16%)
Is a distinction made between interactions of the active principle and those of the group?	5 (83.33%)	9 (50%)	9 (100%)	5 (33.33%)	14 (58.33%)
Good search speed	4 (66.6%)	14 (77.77%)	9 (100%)	9 (60%)	18 (75%)
DID support					
Computer	6 (100%)	12 (66.6%)	8 (88.88%)	10 (66.66%)	18 (75%)
Print	0	6 (33.3%)	1 (11.11%)	5 (33.33%)	6 (25%)
Availability					
Web page	4 (66.6%)	14 (7.77%)	5 (55.55%)	13 (86.66%)	18 (75%)
Book	0	2 (11.11%)	2 (22.22%)	0	2 (8.33%)
CD-ROM	2 (33.3%)	2 (11.11%)	2 (22.22%)	2 (13.33%)	4 (16.66%)

Data represents n (%) of the total of each group.

evidence previously published but those produced ad hoc. For example, Micromedex® classifies as theoretical/probable; Medinteract® classifies as well-documented/documented/scarcely-documented, etc, and makes no reference even to the articles in which the relevant interaction is discussed. All of this, once again, indicates a high level of variability.

It should be noted that all the included DIDs were specific to interactions, whereas many among the excluded DIDs belonged to databases contained a wider range of data. Perhaps in the latter there was less physical space available.

The criteria defined as non-essential were met by a higher number of databases than the minimum criteria. Half the authors or promoters were public and half private; a direct correlation is found between a private background and a higher score (data not shown).

One aspect to emphasise is that some DIDs offer the possibility of seeing the structural features in a preview prior to purchase. It is even possible with some databases to view a sample prior to purchase (Medinteract, Stockley, Lexi). However, others offer up very little information to enable an evaluation prior to a formal purchase (Hansten, Drug Interaction Facts).

The preferred format is a webpage, which is logical as it allows ubiquitous access and constant updating. Book form is bothersome for consulting data, as it is costly to update and is of no use when incorporating data into expert systems. However, book form is the only option for Drug Interaction Facts and Hansten, 2 very reliable and often-cited DIDs.[22,23] This could be due to cultural factors or to a failure to update the format of older DIDs, designed in an age when the criteria were less strict.

The period between updates is specified only in 12 of the 24 DIDs compared, with a very wide range, from immediate updates to a period of three years for each update of the Martindale DID.[24] Update intervals of more than 1 year should not be admissible, and demands should perhaps be made for more frequent DID updates using the Internet. The description of significant interactions detected in clinical studies, concerning commercially-available medicines, and the rapid detection of others during the post-commercialisation phase, make this aspect increasingly important.

Only half of the databases have a multicheck structure, ie, the introduction of several medications at once in order to produce an analysis (a higher proportion among the Spanish and included databases), which seems a low percentage in the era of informatics if they are to be used in clinical practice, where the number of polymedicated patients is constantly increasing. This option is impossible with those databases in book format and is unavailable with two of the most well-known databases, Drug Interaction Facts and Hansten. With Micromedex, this option is only available in addition to payment for the Drugdex® DID.

The only work similar to ours found in the bibliography compared 5 DIDs relating to the United States. The highest-scoring DID is Walgreens, to which we had no access. Medscape and DrugReax achieved high scores, which tallies with our study. However, the second highest scoring database is DrKoop, which was excluded from our study due to not meeting all the minimum essential criteria.

One of the limitations of our work is the possibility of a slant towards detection of Spanish databases in the informal search. An attempt has been made to locate different DIDs which are available on the open market, and analyse their quality from the perspective of a Spanish professional, a method which this publication tries to achieve.

Another possible limitation is the fact that the criteria and weightings used were established by the authors. However, it is worth noting that up to now it has not been possible to find any generally accepted previous classification or evaluation. Minh et al[9] describe content criteria (accuracy, complete data, references, language, and interaction management) and evaluation of usefulness (ease of use, speed, multicheck, multifunctionality). The study, which analysed just 5 DIDs (Drug Pharmacology, DrKoop, Medscape, Walgreens, and DrugReax), uses 9 quality criteria, all with the same value. In our study 20 criteria have been used, of which the following tally with Minh et al: ease of searching, multicheck, multifunctionality, references, language, and interaction management.

The total number of interactions was not considered as a criterion. In our judgement, it is important that a DID contains a large number of interactions. However, when evaluating the possibility of incorporating a DID into educative programmes, electronic prescription systems or a clinical task, it is possible that certainty, clinical significance and help with decision-making are more relevant. Certainty makes reference to the fact that in a medical setting based on evidence, the interaction should have sufficient bibliographical references and the DID authors have classified the interactions according to some scale portraying level of evidence, as is seen in Drug Interaction Facts. The relevance assumes that some scale of severity is used, as can be found in Medinteract or Lexi. The abundance of medicinal interactions leads to, in some clinical practice environments, the need to prioritise attention towards those which are most severe. Particularly with computerised systems, it is necessary to obtain a "good" interaction signal or noise, for which criteria of severity is essential.[25]

Lastly, knowledge of medicinal interaction is especially important if clinical action is to take place in order to prevent its occurrence. For this reason is seems essential for authors that the DIDs include a concrete description of the clinical management of a patient suffering with the relevant interaction, as can be found in, for example, Lexi or Micromedex.

On the other hand, it is true that the scarce number of DIDs which fulfil these criteria could be evidence of an excessive strictness in definition on our part, and that other criteria, as fulfilled in 75% of databases, could be included in more databases in the analysis. However, for the reasons described above, it seemed necessary to require all the DIDs to comply with all of the four selected criteria.

Another important task is to evaluate the clinical significance of each interaction, since no standard protocol could be found for the allocation of such significance. Each DID has its own protocol, as can be seen with Drug Interaction Facts or Hansten, which depends particularly on the severity and scientific evidence of the interaction in question. Recently a study was published which attempted to create a procedure for establishing the clinical significance of interactions.[26] However, the proposal has certain significant problems, such as not accounting for the idiosyncrasy of the patient, not being validated by studies on concrete groups of medicines, and proposing a final ranking based on severity

and documentation. Although this is reasonable, the 2 categories require prior definition. All of this makes difficult the task of creating a standardised procedure for establishing clinical significance.[27]

The wide range of information sources regarding existing medicinal interactions poses a major problem to professionals when compiling and evaluating information regarding a specific interaction coming from a specific source. We therefore consider that this study provides information which could be of interest for the practice of health professionals.

This study provides a basis for a much larger project by the same research team, in which an attempt can be made to evaluate the quality of the content of DIDs, as well as the level of agreement amongst them regarding medications belonging to various therapeutic groups. The important fact is that a database of pharmacological interactions can be very well structured, but the information may be incomplete or not as relevant as it should be. As a result, this primary information, although considered to be of great value, needs to be contrasted with the information analysed regarding the content of each DID, in order to permit a complete and general vision.

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References

1. Rosholm JU, Bjerrum L, Hallas J, Worm J, Gram LF. Polypharmacy and the risk of drug-drug interactions among Danish elderly. Danish Medical Bulletin. 1998;45:210-3.
2. Estudio APEAS: estudio sobre la seguridad de los pacientes en Atención Primaria de Salud. Madrid: Ministerio de Sanidad y Consumo; 2008.
3. Recalde JM, Zunzunegui MV, Beland F. Interacciones de fármacos prescritos en población mayor de 65 años. Aten Primaria. 1998;22:434-9.
4. Michocki RJ, Lamy PP, Hooper FJ, Richardson JP. Drug prescribing for the elderly. Arch Farm Med. 1993;2:441-4.
5. National Prescribing Service. What is polypharmacy? NPS News n.° 13.2000.
6. National Health Service. Medicines for older people. 2001. Department of Health [accessed, May 18, 2007]. Available from: http://www.gov.uk/nsf/olderpeople.htm
7. Calvet A, Díez de Ulzurrun M, Pérez MT, Esteras J. Interacciones farmacológicas en tratamientos crónicos: medidas correctoras para su prevención en un área básica de salud rural. Aten Primaria. 2001;27:33-7.
8. Bermejo Viñedo T, Pérez Menendez Conde C. Aplicación de las nuevas tecnologías a la farmacia hospitalaria en España. Farm Hosp. 2007;31:17-22.
9. Minh VL, McCartGM, Tsourounis C. An assessment of Free, online Drug-Drug Interaction Screening Programs (DSPs). Hospital Pharmacy. 2003;38:662-8.
10. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, van Bergen RC. Concordance of severity ratings provided in tour drug interaction compendia. J Am Pharm Assoc (Wash). 2004;44:136-41.
11. Consejo General de Colegios Ofi ciales de Farmacéuticos. Base de Datos del Conocimiento farmacéutico BOT PLUS [accessed, May 17, 2007]. Available from: www.portalfarma.com
12. XiZ Comunicacion. Medinteract [accessed, May 10, 2007]. Available from: www.medinteract.net
13. Sociedad Española de Farmacia Hospitalaria. Guía de la SEFH [accessed, May 26, 2007]. Available from: www.sefh.es
14. Lexi comp. Lexi-interact [accessed, May 18, 2007]. Available from: www.lexi.com
15. Medscape, Drug Interaction Checker [accessed, May 19, 2007]. Available from: www.medscape.com
16. Hansten PD, Horn JR. Drug Interactions Analysis and Management. St. Louis: Facts and Comparisons; 2007.
17. Thomson Healthcare. Drug-reax [accessed, May 20, 2007]. Available from: www.micromedex.com
18. Stockley IH. Interacciones Farmacológicas. 2nd ed. Barcelona: Pharma Editores; 2006.
19. Tatro DS. Drug Interaction Facts. San Carlos: Facts and Comparisons; 2007.
20. Clauson KA, Seamon MJ, Clauson AS, van TB. Evaluation of drug information databases for personal digital assistans. Am J Health-Syst Pharm. 2004;61:1015-23.
21. Galatti L, Mazzaglia G, Greco A, Sessa E, Cricelli C, Schito GC, et al. Co-prescriptions with itraconazole and fl uconazole as a signal for possible risk of drug-drug interactions: a four-year analysis from Italian general practice. Pharmacoepidemiol Drug Saf. 2007;16:422-8.
22. Katende-Kyenda NL, Lubbe MS, Serfontein JH, Truter I. Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa. Journal of the Medical Association of South Africa. 2008;98:109-13.
23. Sweileh WM, Sawalha AF, Jaradat NA. Extent of potential drug interactions among patients receiving anti-hypertensive medications. Saudi Medical Journal. 2005;26:548-52.
24. Grupo Ars XXI. Martindale [accessed, May 15, 2007]. Available from: www.imedicinas.com
25. Peral Aguirregoitia J, Lertxundi Etxebarria U, Martínez Bengoechea MJ, Mora Atorrasagasti O, Franco Lamela E, Gabilondo Zelaia I. Evaluación prospectiva de interacciones entre medicamentos en pacientes ingresados mediante una aplicación informática. Farm Hosp. 2007;31:99-100.
26. Amariles P, Giraldo NA, Faus MJ. Interacciones medicamentosas: aproximación para establecer y evaluar su relevancia. Med Clin (Barc). 2007;129:27-35.
27. Rodríguez Terol A, Santos Ramos B, Caraballo Camacho MO, Ollero Baturone M. Relevancia clínica de las interacciones medicamentosas. Med Clin (Barc). 2008;130:758-9.
28. Agencia Española del Medicamento. AGEMED [accessed, May 25, 2007]. Available from: www.egemed.es
29. American Society of Health-system pharmacy. American Hospital formulary Service Drug Information [accessed, May 23, 2007]. Available from: www.asph.org
30. Drugdigest. Check Interaction [accessed, May 23, 2007]. Available from: www.drugdigest.org
31. Drugmaster group. Druint software [accessed, May 23, 2007]. Available from: www.drugmastersl.com
32. Drugs.com. Drug Interaction Checker [accessed, May 23, 2007]. Available from: www.drugs.com
33. Epocrates [accessed, May 20, 2007]. Available from: www.epocrates.com

34. Coordinadores de la Agencia española del medicamento y Productos Sanitarios. Guía de Prescripción Terapéutica [accessed, May 23, 2007]. Available from: www.imedicinas.com/GTPage/
35. MedicinNet [accessed, May 27, 2007]. Available from: www.medicinenet.com
36. Servicio Biblioteca Nacional de Medicina [accessed, May 25, 2007]. Available from: www.medlineplus.gov
37. Dr. Koop [accessed, May 24, 2007]. Available from: www.drkoop.com
38. RxList.inc. [accessed, May 23, 2007]. Available from: www.fdb.rxlist.com
39. Grupo Ars XXI. Stockley Alertas; 2007.
40. The medical letter, inc. Adverse drug interaction program [accessed, May 22, 2007]. Available from: www.medicaletter.com
41. Agence Française de Sécurité Sanitarie des Produits de Santé. Thesaurus des interactions Medicamenteus [accessed, May 23, 2007]. Available from: www.agemed.sante.gouv.fr
42. Drug Bank [accessed, Jun 2, 2007]. Available from: www.drugbank.ca
43. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Sto thard P, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006;34:D668-72.
44. Drug Interaction Knowledge-base (DIKB) [accessed, May 24, 2007]. Available from: www.ieeexplore.ieee.org
45. Boyce RD, Collins C, Horn J, Kalet I. Modeling drug mechanism knowledge using evidence and truth maintenance. IEEE Trans Inf Technol Biomed. 2007;11:386-97.
46. Drug Interaction Ontology [accessed, May 28, 2007]. Available from: www.bio.cs.titech.ac.jp
47. Yoshikawa S, Satou K, Konagaya A. Drug interaction ontology (DIO) for inferences of possible drug-drug interactions. Medinfo. 2004;11:454-8.
48. FDA MedWatch database. Department of food and Human Services [accessed, May 26, 2007]. Available from: www.fda.gov
49. Katende-Kyenda NL, Lubbe MS, Serfontein JH, Truter I. Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa. Journal of the Medical Association of South Africa. 2008;98:109-13.
50. General Practice Research Database (GPRD) [accessed, Jun 7, 2007]. Available from: www.gprd.com
51. Hammad TA, Graham DJ, Staffa JA, Kornegay CJ, Dal Pan GJ. Onset of acute myocardial infarction after use of non-steroidal antiinflammatory drugs. Pharmacoepidemiol Drug Saf. 2008;17:315-21.
52. Yang Y, Moir E, Kontopidis G, Taylor P, Wear MA, Malone K, et al. Structure-based discovery of a family of synthetic cyclophilin inhibitors showing a cyclosporin-A phenotype in CaenorhaBDIMtis elegans. Biochem Biophys Res Commun. 2007;363:1013-9.
53. M&T Drug Interaction Database. Department of pharmaceutics. University of Washington [accessed, Jun 5, 2007]. Available from: www.druginteractioninfo.org
54. Ragueneau-Majlessi I, Boulenc X, Rauch C, Hachad H, Levy RH. Quantitative correlations among CYP3A sensitive substrates and inhibitors: literature analysis. Curr Drug Metab. 2007;8:810-4.
55. RAD-AR Council. Anti-hypertensive drug database [accessed, May 25, 2007]. Available from: www.rad-ar.ogr.jp
56. Yoshida M, Matsumoto T, Suzuki T, Kitamura S, Mayama T. Effect of concomitant treatment with a CYP3A4 inhibitor and a calcium channel blocker. Pharmacoepidemiol Drug Saf. 2008;17:70-1.
57. Side Effects software [accessed, May 26, 2007]. Available from: www.sidefx.com
58. Fox GN. Drug interactions software programs. J Fam Pract. 1991;33:273-80.
59. STICH [accessed, May 27, 2007]. Available from: www.stitch.embl.de
60. Kuhn M, von Mering C, Campillos M, Jensen LJ, Bork P. STITCH: interaction networks of chemicals and proteins. Nucleic Acids Res. 2008;36:D684-8.
61. The marine natural products database (MNPD) [accessed, May 27, 2007]. Available from: www.dmnp.chemnetbase.com
62. Liu B, Zhou J. SARS-CoV protease inhibitors design using virtual screening method from natural products libraries. J Comput Chem. 2005;26:484-90.
63. The traditional Chinese medicines database (TCMD) [accessed, May 30, 2007]. Available from: www.gfmer.ch
64. Veteran Health Administration (VHA) clinical database. Department of Veterans Affairs [accessed, May 20, 2007]. Available from: www.va.gov
65. French DD, Margo CE. Post-marketing surveillance of ischaemic optic neuropathy in male veterans co-prescribed phosphodiesterase-5 inhibitors with organic nitrates or alpha-blockers. Drug Saf. 2008;31:241-7.
66. Janchawee B, Wongpoowarak W, Owatranporn T, Chongsuvivatwong V. Pharmacoepidemiologic study of potential drug interactions in outpatients of a university hospital in Thailand. J Clin Pharm Ther. 2005;30:13-20.
67. British National Formulary. BNF Group [accessed, Jul 30, 2007]. Available from: www.bnf.org
68. Tavassoli N, Sommet A, Lapeyre-Mestre M, Bagheri H, Montrastruc JL. Drug interactions with cholinesterase inhibitors: an analysis of the French pharmacovigilance database and a comparison of two national drug formularies (Vidal, British National Formulary). Drug Saf. 2007;30:1063-71.
69. Mellbye KS, Berg C. Heavy consumers of drugs –seen from the viewpoint of the community pharmacist. Tidsskr Nor Laegeforen. 2004;124:3069-71.
70. Nielsen EW, Dybwik K. Drug interactions in an intensive care unit. Tidsskr Nor Laegeforen. 2004;124:2907-8.
71. Guedon-Moreau L, Ducrocq D, Duc MF, Quieureux Y, L'Hote C, Deligne J, et al. Absolute contraindications in relation to potencial drug interactions in outpatient prescriptions: analysis of the first five million prescriptions in 1999. Eur J Clin Pharmacol. 2003;59:689-95.
72. Galatti L, Mazzaglia G, Greco A, Sessa E, Cricelli C, Schito GC, et al. Co-prescriptions with itraconazole and fl uconazole as a signal for possible risk of drug-drug interactions: a four-year analysis from Italian general practice. Pharmacoepidemiol Drug Saf. 2007;16:422-8.
73. Trifiro G, Corrao S, Alacqua M, Moretti S, Tari M, Caputi AP, et al. Interaction risk with proton pump inhibitors in general practice: signifi cant disagreement between different drug-related information sources. Br J Clin Pharmacol. 2006;62: 582-90.
74. Hohl CM, Dankoff J, Colacone A, Afi lalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001;38:666-71.
75. Vroom F, van Roon EN, van den Berg PB, Brouwers JR, de Jong-van den Berg LT. Prescribing of sulfasalazine, azathioprine and methotrexate round pregnancy –a descriptive study. Pharmacoepidemiol Drug Saf. 2008;17:52-61.
76. Walgreens.com [accessed, May 28, 2007]. Available from: www.walgreens.com
77. A2Z Drugs [accessed, Jun 3, 2007]. Available from: www.az2drugs.com
78. Clauson KA, Seamon MJ, Clauson AS, van TB. Evaluation of drug information databases for personal digital assistants. Am J Health Syst Pharm. 2004;61:1015-24.
79. Clinical Pharmacology on hand [accessed, Jun 2, 2007]. Available from: www.cponhand.gsm.com
80. PDR. Drug Interaction [accessed, May 25, 2007]. Available from: www.pdr.net
81. Tarascon Pocket Pharmacopoeia [accessed, May 25, 2007]. Available from: www.tarascon.com
82. Triple Prescribing Guide [accessed, Jun 3, 2007]. Available from: www.pharmscope.com

Appendix 1 Databases not included

Database	Reason for exclusion	Citation or location
No application in clinical practice		
Drug Bank[42]	Database for the prediction of potential medicinal interactions in the context of research and development of new drugs by the pharmaceutical industry	Wishart et al[43]
Drug Interaction Knowledge-base (DIKB)[44]	DID for the development of new drugs	
Drug Interaction Ontology (DIO)[46]	A system which raises a hypotheses regarding new interactions according to molecular structure of the active principles	Yoshikawa et al[47]
FDA MedWatch database[48]	Not a database of interactions, but a collection of clinical cases	Katende et al[49]
General Practice Research Database (GPRD)[50]	System for the collection of information regarding the population of the United Kingdom	Hammad et al[51]
LIDAEUS	DID of molecules which interact with proteins	Yang et al[52]
M&T Drug Interaction Database[53]	DID which collects clinical studies	Ragueneau et al[54]
RAD-AR Council. Anti-hypertensive drug database[55]	Relating only to one medicine group. Not a DID specific to interactions between drugs, but a dissemination database for the correct use of medications	Yoshida et al[56]
Side Effects software[57]	Database concerning adverse effects of drugs	Fox[58]
Stitch "search tool for interactions of chemicals and proteins"[59]	STITCH is a resource for studying and predicting known interactions in chemical products and proteins	Kuhn et al[60]
The marine and natural products database (MNPD))[61]	Database of natural product	Liu et al[62]
The traditional Chinese medicines database (TCMD)[63]	Database of natural product	Liu et al[62]
Veteran Health Administration (VHA) clinical database[64]	Not a database of interactions, but an information and consultation network for patients and patient data exploitation	French et al[65]
Not accessible		
Prince of Songkla University Hospital interactions database		Janchawee et al[66]
British National Formulary[67]		Tavassoli et al[68]
Drug Interaction III		Fox[58]
DRUID		Mellbye et al[69]; Nielsen et al[70]
French Farmacovigilance Database		Tavassoli et al[68]
French healthcare database		Guedon et al[71]
French National Formulary		Tavassoli et al[68]
Italian Pharmaceutical Repertory (REFI)	Articles citing this DID were found, but not the DID itself	Galatti et al[72]
Italian Summary of Product Characteristics (SPC) of PPI and Drugdex information		Trifiro et al[73]
PharmVigilance		Hohl et al[74]
Pregnancy-interaction database		Vroom et al[75]
Walgreens.com[76]		Minh et al[9]
BDIM para PDA		
A2Z Drugs[77]		Clauson et al[78]
Clinical Pharmacology on hand[79]		Clauson et al[78]
PDR. Drug Interaction[80]		Fox[58]
Tarascon Pocket Pharmacopoeia[81]		Clauson et al[78]
Triple i Prescribing Guide[82]		Clauson et al[78]

DID indicates drug interaction database.
References in the first column correspond to the DID location. References in the third column correspond to the article which cites the DID.