

Special Article

Prescribing information in 26 countries: a comparative study

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Abstract This study was set up to document the variability of prescribing information from different sources concerning indications, side effects and cautions of selected drugs. An original method to measure the degree of information agreement among different written materials, such as summaries of product characteristics, package inserts and data sheets, and a widely accepted reference text was developed. The results show that there is substantial disagreement in the materials available to prescribers and patients in different countries. Disagreement was even found within a single country when written materials from different

brands of the same drug were compared. The discordance can be explained by the fact that the evidence available for each drug is considered/assessed differently by separate countries. It is argued that the discrepancies found may mislead prescribers, patients and those comparing drug-use patterns across countries. National regulatory authorities have a key role to play in remedying this situation, and a two-pronged approach is proposed. At the international level, national authorities should strengthen collaboration and information interchange and, at the national level, should implement appropriate measures aimed at removing contradictory statements on drug-information materials that have no reason to be different. Finally, further training and continued education aimed at drug regulatory officials could provide the necessary knowledge and enable national authorities to meet the need for drug information that is independent of commercial interests.

Keywords Drug information · Regulatory affairs · International survey

Members of *The International Comparative Study On Drug Information (ICSODI) Collaborative Group* are listed at the end of the paper.

Introduction

The authors have been involved for several years in activities related to the work of national drug regulatory authorities in many countries. Regulatory requirements concerning the information to be made available to professionals and patients may differ considerably from one country to another. Direct experience has revealed that the actual implementation of such regulatory requirements is also different in different countries because of resource limitations. Differences that were felt to be important in the information made available to prescribers and patients in different countries were identified. Published studies addressing drug information in general [1, 2, 3, 4] and readability of patient information materials [5, 6, 7] were found, but very little [8] was found specifically addressing the issue of documenting differences in key aspects of drug information among different countries for the same drugs. To address the need for assessing these differences with a systematic approach, a collaborative, international comparative study on available information to analyse the variability of written drug information, such as summaries of product characteristics, in different countries and within single countries was set up. This paper reports a first set of findings and their analysis.

Materials and methods

Materials

Six drugs were selected among those meeting at least one of the following criteria: the drug was well known and widely used, presented a different problem profile depending on the clinical setting in which it was used and was marketed relatively recently. Consumption was not considered because reliable data are not always available and, even when available, differences among countries do not allow for the identification of a clear-cut 'most consumed drug'. Based on these criteria, celecoxib, ciprofloxacin, cisapride, fluoxetine, montelukast and nifedipine were initially selected, but enough usable data could be obtained for only three of these: ciprofloxacin, fluoxetine and nifedipine. The main reason for the lack of information materials on the other three was that they were not marketed during the survey period in all the countries considered. However, the three drugs investigated were among the top 30 drugs in terms of global sales in 2000 [9] and covered three therapeutic areas of high world-wide relevance in terms of mortality and morbidity [10].

Written information materials approved by national regulatory authorities were collected in countries where such materials exist (e.g. summaries of product characteristics, such as those as approved by European authorities). In countries where the national regulatory authority does not approve drug information documents (or when these could not be obtained for the study), only prescribing information materials available to health professionals and patients were collected. The latter were materials such as package inserts or data sheets in commercially available compendia like MIMS, prepared and published by or on behalf of the company holding the marketing authorisation.

Thus, in all, 483 written materials were obtained from the 26 countries and analysed. The international comparison presented is based on 78 of the written materials: one per drug from each of the 26 countries (Fig. 1). In order to be able to measure the greatest amount of information in the compendia materials, only one material per country per drug was compared and material originating from the same company was used as often as possible. In the few cases in which material from the same company was not available (Table 1), the next most complete available documentation was used.

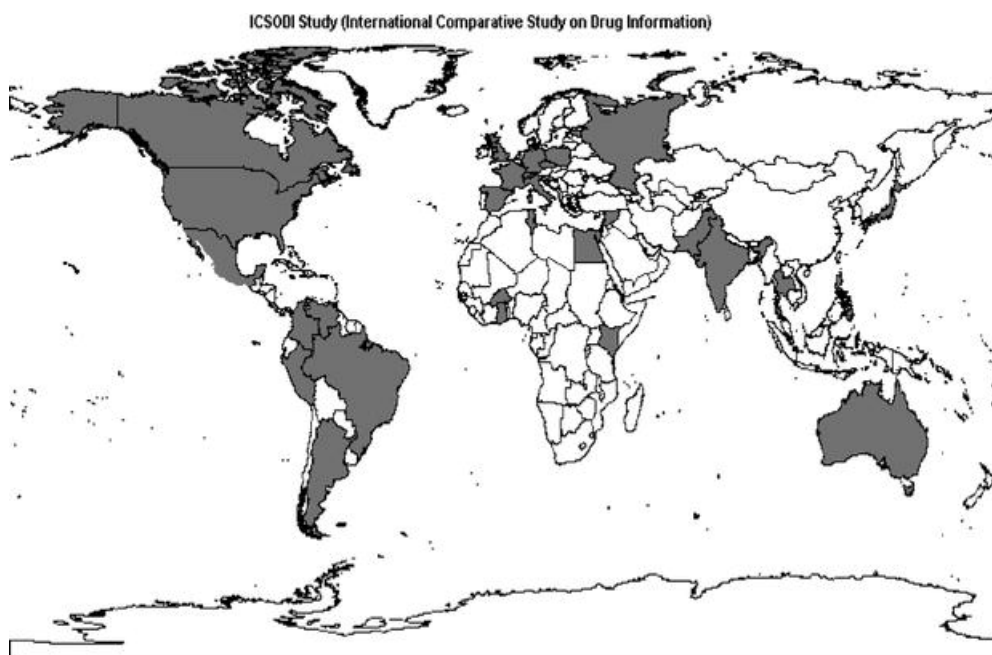


Fig. 1. Geographic distribution of the 26 participating countries: America 8, Europe 8, Africa 4, Asia & Australasia 6

[Table 1. will appear here. See end of document.]

The intra-country comparison is based on 42 written materials (6 for ciprofloxacin, 20 for fluoxetine and 16 for nifedipine) approved by the national regulatory authority of one of the 26 countries.

Methods

Four variables were considered: indications, dosage range in adults, side effects, and cautions. For these variables, a checklist of items was created (37 for ciprofloxacin, 48 for fluoxetine, and 22 for nifedipine; Table 2) using the British National Formulary (BNF 40, September 2000) [11] as a reference text. The BNF was chosen because it has a world-wide reputation for being a complete, independent, reliable and practice-oriented source of information. Furthermore, the BNF is widely used by professionals around the world because it is easy to obtain and inexpensive. The BNF September 2000 issue was used because it was contemporary to the materials collected. Side effects and adverse drug reactions were arbitrarily grouped into one variable called side effects (as in the BNF). For the comparison study, only those side effects that were either frequent or severe were considered. In order to be considered frequent, side effects had to be reported as appearing in at least 1% of patients, according to the AHFS 2001 [12]. To be considered severe, side effects had to fit the criteria published

by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden (<http://www.who-umc.org/umc.html>). Thus, the variable called ‘side effects’ actually involved ‘frequent and/or severe side effects and adverse drug reactions’. Similarly, both cautions and contra-indications were grouped into one variable called ‘cautions’.

[Table 2. will appear here. See end of document.]

For each country, drug and variable, the checklist was compared with the materials collected in order to obtain the number of checklist items found in the materials. The statements found in the collected materials that were not mentioned in the BNF were not considered. Since no complete agreement between any of the materials was found (see Results), an indicator for the proportion of agreement was developed so that the results could be ranked within a range from maximum (rather than complete) to minimum agreement. The indicator was called “degree of information agreement” and was calculated for indications, side effects and cautions for each country and drug. To do this, the proportion of the number of checklist items found in the materials against the total number of relevant checklist items was first calculated. The mean and the 95% confidence interval (CI) for the proportions were then calculated. A “1” was assigned to the degree of information agreement when the proportion of checklist items found was greater than or equal to the higher CI, a “0” was given for proportions within CI, and a “-1” for proportions less than or equal to the lower CI. The dose range in adults was considered as a dichotomous variable (yes/no) and 1 point was assigned if it was in agreement with the range given in the BNF (i.e. both minimum and maximum dose within range) or 0 if it wasn’t. Thus, the sum of the individual scores of the four variables could range from 4 (maximum agreement) to -3 (minimum agreement) for each material analysed.

The same checklist and methodological approach used in the inter-country evaluation was also applied when doing comparisons among materials collected from an individual country. One country was selected because of the large number of items available for the comparison and for the completeness of the materials provided.

Results

Table 1 describes the findings concerning the inter-country comparisons. The information materials collected and analysed referred to products from the same company in 20 countries for nifedipine, 21 for fluoxetine and 22 countries for ciprofloxacin. The marketing

authorisation year was substantially homogeneous for the 26 countries. Drug information materials approved at the time the marketing authorisation was issued were available for 14 countries for ciprofloxacin and 18 for fluoxetine and nifedipine.

Table 3 shows the comparison between the information stated in the BNF and that found in the materials collected. Of 26 countries, 11 had information that matched BNF indications for nifedipine. Only materials from Colombia and the UK listed all the indications included in the BNF for ciprofloxacin, and those from Canada, Estonia and the UK for fluoxetine. Concerning ciprofloxacin, materials from 3 countries are in disagreement with the dose range recommended by the BNF. This disagreement involved a total of 7 countries for nifedipine and 9 for fluoxetine, i.e. over one-third of the sample. None of the materials from the various countries reports all major side effects listed in the BNF for ciprofloxacin and fluoxetine. Concerning nifedipine, only materials from Spain were found to report all the side effects reported in the BNF, while materials from Colombia did not report any of the 7 major side effects included in the BNF. Again, none of the materials from any of the countries reported all the cautions included in the BNF. The findings of this study include extremes such as the presence of 1 caution statement from the 19 listed in the BNF for ciprofloxacin in the Philippines, 1 of 11 for fluoxetine in Argentina, and 3 of 12 for nifedipine in Mozambique and Poland.

[Table 3. will appear here. See end of document.]

Table 4 reports the degrees of disagreement for each drug, country and variable. Table 5 shows the overall (i.e. grouping all variables) adherence of national materials with BNF statements. Besides the expected high agreement of materials from the United Kingdom (although never complete) for the three drugs, only Italy and the USA showed a high proportion of agreement for at least two drugs. Strong disagreement was found for fluoxetine in Argentina, Egypt, India and Tunisia and for nifedipine in the Philippines and Venezuela. However, a large inter-drug variability was observed, since countries with a high proportion of agreement for one drug showed low proportion for another (e.g. India: ciprofloxacin vs fluoxetine; Philippines: fluoxetine vs nifedipine).

[Table 4. will appear here. See end of document.]

[Table 5. will appear here. See end of document.]

Table 6 reports the findings on the 38 materials from one country used for the intra-country part of the analysis. While for most products each company had only one brand name, two

companies marketed their products under two different brand names for fluoxetine and one company for nifedipine.

[Table 6. will appear here. See end of document.]

Table 7 reports the individual results. The overall picture of the degree of information agreement for all four variables is substantially similar to that found in the inter-country comparisons. Findings concerning side effects and cautions for ciprofloxacin and fluoxetine showed that the majority of collected materials were in extremely low agreement with BNF statements. Although the detailed results on materials for other countries are not reported in this paper, we found that most countries demonstrate a substantially similar picture to that presented here—which is the main reason that makes it unnecessary to disclose the name of the country.

[Table 7. will appear here. See end of document.]

Discussion

Looking at inter-country comparisons, the degree of information agreement is surprisingly low for drugs that are routinely used in large numbers of patients. The disparity of dose ranges recommended by the different sources is especially surprising. Theoretically, prescribing information is based on the assessment of clinical studies and post-marketing surveillance activities. In the majority of the cases studied, the materials collected were related to products of the same mother company, thus leading to the assumption that the same basic facts should have been used to make the decisions concerning indications, dosage, side effects and cautions. However, the results show that prescribers and patients are recommended substantially different things in different countries, and this may be due to the fact that the national authority does not conduct a full and systematic assessment of available world-wide data concerning clinical studies and drug monitoring data before approving prescribing information materials.

If intra-country comparisons are examined, the picture becomes even more difficult to understand: why should products have different indications, dosages, side effects and cautions simply because they have a different brand name? While a plausible explanation cannot be offered for the differences found, it is assumable that the implications of disagreement between prescribing information materials at the national level can be serious for patients and for those engaged in activities aimed at ensuring rational drug use. These implications

can also involve communication problems among prescribers, regulatory authorities, companies and patients. At the international level, there can be serious implications for patients travelling, as well as for health workers comparing drug utilisation patterns or developing therapeutic guidelines.

When the safety information of the drugs studied was examined, it often resulted simply as a list, without frequency indications or any specific guidance for prescribers or patients. It is unlikely that any prescriber be able to remember dozens of side effects and adverse reactions related to a drug, especially when their severity or likelihood are not specified. However, patients presented with a list of side effects that is much richer than the list of expected benefits may either be reluctant to take a drug or decide that caution messages are grossly exaggerated and that they deserve to be disregarded. This leads one to conclude that such extensive lists lacking practical guidance are probably not quite so useful to either prescribers or patients. It is urgent for companies and regulatory authorities to develop ways to present safety information that actually help prescribers or patients to make better choices and to take action when specific signs appear. Until such ways are found and implemented, some will be left with the impression that safety information is provided merely to comply with a requirement or to limit liability.

An intriguing finding concerns nifedipine's indication for Raynaud's phenomenon. Although invariably present in industrialised countries, this indication is often missing in developing countries and is actually the most frequent cause of disagreement between the BNF and the collected materials for dose and indications. Although a recently published meta-analysis questions the consistency of clinical studies supporting nifedipine's efficacy in Raynaud's phenomenon [13], it is difficult to understand why a company would renounce approval of an indication (for a world-wide disease), especially in the south of the world, when that indication has already been approved in the north.

In the end, all considerations seem to lead invariably to the role of national regulatory authorities. Deciding on the contents of drug information materials is their responsibility. Their task is difficult, especially when resources are limited and companies submit large amounts of different materials to different countries. It is difficult to know whether pharmaceutical companies have more to gain or lose from the situation of substantial international and sometimes national disagreement in drug information materials. It is very likely that some of them have contributed to creating it. Yet, the authors tend to believe that the key role for a rational solution remains with the national authorities. The very first step

in the right direction is to become aware of the situation and of its implications in terms of patient safety, rational drug use, and credibility of the regulatory work.

In modern times, where it is very easy to access incredible amounts of information and where standardisation has reached its highest peak in all areas (from fast food to architecture and electronics), it should not be extremely difficult for national authorities to identify sources of drug information that can be used, as a complement to documentation submitted by interested parties, to produce locally valid materials. Finally, there are “simple” measures that could dramatically increase the degree of information agreement between information materials at the national level. One example is to implement a measure already in use in some countries, which consists of requiring that prescribing information for all pharmaceutical equivalents be the same as that approved for a reference drug.

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Appendix

Contributors

L. Rãgo and V. Reggi developed the initiative, and with R. Balocco-Mattavelli, M. Bonati, A. Figueras and C. Kopp designed the study. V. Reggi, R. Balocco-Mattavelli, M. Bonati, A. Figueras and C. Kopp wrote the initial protocol and drafted the operations manual. R. Balocco-Mattavelli and E. Jambert obtained the material. I. Breton, E. Jambert, E. Montaner and F. Rocchi organised the materials, constructed and maintained the database, and did the analyses with M. Bonati, V. Reggi and A. Figueras, who supervised the process of work. The co-ordinating group read and commented on the paper, which was jointly written with the collaboration of C. Pandolfini. M. Bonati will act as guarantor for the paper.

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Table 1. Baseline characteristics of evaluated materials (26 countries)

	Ciprofloxacin	Fluoxetine	Nifedipine
	(500 mg)	(20 mg)	(10–20 mg)
Companies (no.)	5 different (Bayer in 22 countries)	6 different (Ely Lilly in 21 countries)	7 different (Bayer in 20 countries)
Year of marketing authorisation	1987–1999	1987–2000	1976–1999
Range	1994	1992	1991
Median	14	18	18
Approved material	12	8	8
Yes			
No			

Table 2. British National Formulary-derived checklist (107 items) for assessing agreement of drug information material

	Ciprofloxacin (500 mg)	Fluoxetine (20 mg)	Nifedipine (20 mg)
Indications	Respiratory tract infections, urinary tract infections, chronic prostatitis, gonorrhoea, pseudomonas lower respiratory tract infection in cystic fibrosis, gastrointestinal infection (including typhoid fever), septicemia caused by sensitive organisms, surgical prophylaxis, corneal ulcers, skin and soft-tissue infections	Depressive illness, bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder	Prophylaxis of angina, hypertension, Raynaud's phenomenon
Dose (oral, daily, adults)	500–1500 mg	20–60 mg	15–80 mg
Side effects	Nausea, diarrhoea, vomiting, abdominal pain, jaundice, hepatitis with necrosis, headache, restlessness, Stevens Johnson Syndrome, haemorrhagic bullae, toxic epidermal necrolysis, increase in blood urea and creatinine, hepatic dysfunction (increased serum concentrations of AST and ALT), renal failure, convulsions, hypersensitivity reactions, tendon inflammation and damage	Hypersensitivity reactions (angioedema, urticaria, anaphylaxis, pharyngitis, pulmonary inflammation or fibrosis, arthralgia, myalgia, serum sickness), nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, sexual dysfunction, sweating, dry mouth, tremor, nervousness, insomnia, anxiety, headache, lightheadedness, dizziness, suicidal ideation, anorexia with weight loss, movement disorders and dyskinesias, fever, anaemia, convulsion, neuroleptic malignant syndrome-like event, aplastic cerebrovascular accident, eosinophilic pneumonia, gastrointestinal haemorrhage, pancreatitis, pancytopenia, thrombocytopenia, thrombocytopenic purpura, violent behaviour	Headache, flushing, dizziness, gravitational oedema, exaggerated fall in blood pressure and reflex tachycardia which may lead to myocardial ischaemia, or cerebrovascular ischaemia (short acting preparation), nausea
Cautions	Pregnancy, breast-feeding, children and adolescents, photosensitivity, renal impairment, history of epilepsy, avoid excessive alkalinity of urine, G6PD deficiency, myasthenia gravis	Maniac phase, epilepsy, hepatic impairment, renal impairment, pregnancy, breast-feeding, concurrent electroconvulsive therapy, cardiac disease, history of bleeding disorders, skilled tasks (impairment), avoid abrupt withdrawal	Advanced aortic stenosis, myocardial infarction within 1 month, unstable or acute attacks of angina, porphyria, severe hypotension, pregnancy, heart failure, breast-feeding, hepatic impairment, diabetes mellitus, ischaemic pain, avoid grapefruit juice

Table 3. British National Formulary (BNF) information found in the materials analysed

Drug	Indications	Dose (adult)	Side effects	Cautions
Ciprofloxacin (500 mg)	Number of BNF statements	200–1500 mg	17	9
	Materials: range		5–16	1–7
	Materials: median		12.5	5
	Countries in full agreement	23	None	None
Fluoxetine (20 mg)	Number of BNF statements	20–60 mg	32	11
	Materials: range		0–31	0–9
	Materials: median		14.5	5.5
	Countries in full agreement	3 (Canada, Estonia, UK)	None	None
Nifedipine (20 mg)	Number of BNF statements	15–80 mg	7	12
	Materials: range		0–7	3–10
	Materials: median		4.5	6
	Countries in full agreement	11	1 (Spain)	None

Table 4. Results from the use of the checklist assessing the adherence of national materials with the British National Formulary. Expected sum value is 26 for the first four columns and 104 (i.e. 26×4) for the fifth column

Ciprofloxacin					
Country	Indications	Dose	Side effects	Cautions	Sum
United Kingdom	1	1	1	1	4
India	0	1	1	1	3
Switzerland	0	1	1	1	3
United States	0	1	1	1	3
Australia	-1	1	1	1	2
Brazil	-1	1	1	1	2
Canada	0	1	1	0	2
Italy	0	0	1	1	2
Philippines	1	1	1	-1	2
Spain	0	1	0	1	2
Tunisia	1	1	1	-1	2
France	0	0	0	1	1
Pakistan	0	1	-1	1	1
Syria	0	1	-1	1	1
Thailand	0	1	1	-1	1
Colombia	1	1	-1	-1	0
Croatia	1	1	-1	-1	0
Estonia	-1	1	1	-1	0
Kenya	1	0	0	-1	0
Mexico	0	1	-1	0	0
Poland	-1	1	1	-1	0
Argentina	0	1	-1	-1	-1
Egypt	0	1	-1	-1	-1
Mozambique	-1	1	0	-1	-1
Peru	-1	1	-1	0	-1
Venezuela	0	1	-1	-1	-1

Sum	0	23	4	-1	26
Fluoxetine					
Estonia	1	1	1	1	4
Italy	1	1	1	1	4
Thailand	1	1	1	1	4
Colombia	1	1	1	0	3
Philippines	1	0	1	1	3
United Kingdom	1	1	0	1	3
United States	1	0	1	1	3
Kenya	1	1	1	-1	2
Mexico	1	1	0	0	2
Pakistan	1	1	-1	1	2
Australia	-1	0	1	1	1
Brazil	1	1	0	-1	1
France	-1	1	0	1	1
Poland	1	1	0	-1	1
Spain	1	1	-1	0	1
Canada	1	0	0	-1	0
Croatia	1	0	0	-1	0
Peru	1	0	-1	0	0
Switzerland	-1	0	1	0	0
Venezuela	1	1	-1	-1	0
Mozambique	-1	1	-1	0	-1
Syria	-1	1	-1	0	-1
Argentina	-1	1	-1	-1	-2
India	-1	0	-1	0	-2
Tunisia	-1	1	-1	-1	-2
Egypt	-1	1	-1	-1	-2
Sum	8	18	-1	0	25
Nifedipine					
Australia	0	1	1	1	3

Italy	0	1	1	1	1	3
Mexico	0	1	1	1	1	3
Spain	0	1	1	1	1	3
United Kingdom	0	1	1	1	1	3
Brazil	0	1	1	-1	-1	1
Canada	0	0	1	1	1	1
Egypt	0	1	0	0	0	1
Kenya	0	1	-1	1	1	1
Thailand	0	1	-1	1	1	1
Tunisia	0	1	0	0	0	1
United States	0	0	1	0	0	1
Argentina	0	1	-1	0	0	0
Croatia	1	1	-1	-1	-1	0
Estonia	0	1	-1	0	0	0
France	-1	1	0	0	0	0
Pakistan	1	1	-1	-1	-1	0
Peru	0	0	1	-1	-1	0
Switzerland	0	1	-1	0	0	0
Syria	0	1	-1	0	0	0
Colombia	0	0	-1	0	0	-1
India	-1	1	-1	0	0	-1
Mozambique	0	1	-1	-1	-1	-1
Poland	0	0	0	-1	-1	-1
Philippines	0	0	-1	-1	-1	-2
Venezuela	0	0	-1	-1	-1	-2
Sum	0	19	-5	0	0	14

Table 5. Overall adherence of national materials with British National Formulary (BNF) statements. High: agreement ≥ 3 , Low: agreement ≤ -2 (see Methods and Appendix B for details)

Ciprofloxacin (500 mg)	High	India, Switzerland, United Kingdom, United States
	Low	-
Fluoxetine (20 mg)	High	Colombia, Estonia, Italy, Philippines, Thailand, United Kingdom, United States
	Low	Argentina, Egypt, India, Tunisia
Nifedipine (20 mg)	High	Australia, Italy, Mexico, Spain, United Kingdom
	Low	Philippines, Venezuela

Table 6. Baseline characteristics, agreement and overall adherence with British National Formulary (BNF) of materials from one country

	Ciprofloxacin (500 mg)	Fluoxetine (20 mg)	Nifedipine (10–20 mg)
Baseline characteristics			
Brand names	No. 6	20	16
Companies	No. 6	18	15
Year of marketing authorisation	Range 1988–2000	1991–1999	1980–2000
	Median 1997	1997	1993
BNF information found in the materials analysed			
Indications			
No. of BNF statements	4	3	
Found in the materials:			
	Range; median 4–8; 5	1–3; 1	1–3; 2
Dose (adult)	200–1500 mg	20–60 mg	15–80 mg
No. in agreement	6	20	16
Side effects			
No. of BNF statements	17	32	7
Found in the materials:			
	Range; median 0–14; 4,5	0–31; 0,5	0–5; 4,5
Cautions			
No. of BNF statements	9	11	12
Found in the materials:			
	Range; median 3–7; 4	0–7; 1	1–10; 3
Overall adherence with BNF*			
High	Cyprobay	Prozac, Deproxin, Fluoxetine, Nifedipin, Nifedipine, Fluzac, Magrilan	
Low	–	–	–

*High: agreement ≥ 3 , Low: agreement ≤ 2 (see Methods and Appendix C for details)

Table 7. Results from the use of the checklist assessing the adherence of materials from one country with the British National Formulary. Expected sum values: Ciprofloxacin = 6 in the first 4 columns and 24 for the fifth column. Fluoxetine = 20 in the first 4 columns and 80 for the fifth column. Nifedipine = 12 in the first 4 columns and 48 for the fifth column

Ciprofloxacin	Indications	Dose	Side effects	Cautions	Sum
Cyrobay	1	1	1	0	3
Cipon	1	1	0	0	2
Hipro forte	-1	1	0	1	1
Cifran	0	1	0	-1	0
Ciflocin	-1	1	0	0	0
Ciproxyl	-1	1	-1	0	-1
Sum	-1	6	0	0	5
Fluoxetine					
Prozac	1	1	1	1	4
Deproxin	0	1	1	1	3
Fluxetin	0	1	1	1	3
Fluzac	0	1	1	1	3
Magrilan	0	1	1	1	3
ATD	0	1	1	0	2
Flusac	0	1	0	1	2
Prodep	0	1	1	0	2
Fluoxan	0	1	0	0	1
Fluoxine	0	1	-1	0	0
Flutine	0	1	-1	0	0
Fluxetil	0	1	0	-1	0
Xetin	0	1	-1	0	0
Anzac	0	1	-1	-1	-1
Fluoxetine	0	1	-1	-1	-1
Loxetine	0	1	-1	-1	-1

Oxetine	0	1	-1	-1	-1	-1
Oxsac	0	1	-1	-1	-1	-1
Unprozy	0	1	-1	-1	-1	-1
Flumed	0	1	-1	-1	-1	-1
Sum	1	20	-3	-2	16	16
Nifedipine						
Nifedipin K	1	1	1	1	4	4
Nifedipine	0	1	1	1	3	3
Adalat	0	1	0	1	2	2
Servidipine	0	1	1	0	2	2
Coracten	0	1	1	0	2	2
Nicardia	0	1	1	0	2	2
Nifelat	1	1	-1	0	1	1
Nifelat Q	1	1	-1	0	1	1
Zenusin	-1	1	1	0	1	1
Niefax	0	1	1	-1	1	1
Carnif	0	1	0	-1	0	0
Nelapine	-1	1	1	-1	0	0
Nifecard	0	1	0	-1	0	0
Nifiran	0	1	0	-1	0	0
Calgigard	0	1	-1	-1	-1	-1
Fenamom	0	1	-1	-1	-1	-1
Sum	1	16	4	-4	17	17