Carla Pires[I]

Marina Vigário[II]

Afonso Cavaco[III]

Readability of medicinal package leaflets: a systematic review

Legibilidade das bulas dos medicamentos: revisão sistemática

ABSTRACT

OBJECTIVE: To review studies on the readability of package leaflets of medicinal products for human use.

METHODS: We conducted a systematic literature review between 2008 and 2013 using the keywords "Readability and Package Leaflet" and "Readability and Package Insert" in the academic search engine *Biblioteca do Conhecimento Online,* comprising different bibliographic resources/databases. The preferred reporting items for systematic reviews and meta-analyses criteria were applied to prepare the draft of the report. Quantitative and qualitative original studies were included. Opinion or review studies not written in English, Portuguese, Italian, French, or Spanish were excluded.

RESULTS: We identified 202 studies, of which 180 were excluded and 22 were enrolled [two enrolling healthcare professionals, 10 enrolling other type of participants (including patients), three focused on adverse reactions, and 7 descriptive studies]. The package leaflets presented various readability problems, such as complex and difficult to understand texts, small font size, or few illustrations. The main methods to assess the readability of the package leaflet were usability tests or legibility formulae. Limitations with these methods included reduced number of participants; lack of readability formulas specifically validated for specific languages (e.g., Portuguese); and absence of an assessment on patients literacy, health knowledge, cognitive skills, levels of satisfaction, and opinions.

CONCLUSIONS: Overall, the package leaflets presented various readability problems. In this review, some methodological limitations were identified, including the participation of a limited number of patients and healthcare professionals, the absence of prior assessments of participant literacy, humor or sense of satisfaction, or the predominance of studies not based on role-plays about the use of medicines. These limitations should be avoided in future studies and be considered when interpreting the results.

DESCRIPTORS: Medicine Package Inserts. Comprehension. Consumer Health Information. Review.

[I] Programa de Pós-Graduação – Doutoramento em Sócio-Farmácia. Departamento de Sócio-Farmácia Instituto de Investigação do Medicamento. Faculdade de Farmácia. Universidade de Lisboa. Lisboa, Portugal

[II] Departamento de Linguística. Faculdade de Letras. Universidade de Lisboa. Lisboa, Portugal

[III] Departamento de Sócio-Farmácia. Faculdade de Farmácia. Instituto de Investigação do Medicamento. Universidade de Lisboa. Lisboa, Portugal

Correspondence:
Afonso Cavaco
Faculdade de Farmácia
Universidade de Lisboa
Av. Prof. Gama Pinto
1649-003 Lisboa, Portugal
E-mail: acavaco@ff.ul.pt

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RESUMO

OBJECTIVO: Analisar a literatura sobre legibilidade das bulas dos medicamentos para uso humano.

MÉTODOS: Estudo de revisão sistemática, utilizando as palavras-chave "Readability and Package Leaflet" e "Readability and Package Insert"e a ferramenta de busca académica *b-on*, que contém diferentes bases bibliográficas. O período analisado foi entre 2008 e 2013. Foram aplicados os critérios PRISMA para redigir o relatório da revisão. Foram incluídos artigos originais de pesquisa quantitativa ou qualitativa. Os critérios de exclusão foram: artigos de opinião ou de revisão, ou escritos numa língua diferente do inglês, português, italiano, francês ou espanhol.

RESULTADOS: Foram identificados 202 trabalhos, dos quais 180 foram excluídos e 22 selecionados para análise: dois com profissionais de saúde, 10 com pacientes, três sobre reações adversas e sete descritivos. As bulas apresentaram diversos problemas de legibilidade, entre os quais: textos insuficientemente claros e simples, utilização de tamanhos de letra pequenos e número reduzido de ilustrações. Os principais métodos utilizados para avaliar a legibilidade das bulas foram as fórmulas e os testes de legibilidade/usabilidade. Entre as limitações metodológicas, foram identificados aspetos como o recurso a amostras pequenas, a inexistência de fórmulas de legibilidade específicas para a língua em causa, e.g., português, e a realização de testes de compreensão em grupos de pacientes sem avaliação prévia da literacia, dos conhecimentos específicos na área da saúde, das capacidades cognitivas, ou do grau de satisfação dos participantes.

CONCLUSÕES: Em geral, as bulas apresentaram diversos problemas de legibilidade. Adicionalmente, nesta revisão foram identificadas algumas limitações metodológicas nos estudos revistos (e.g. a participação de um número reduzido de pacientes e profissionais de saúde, a ausência da avaliação prévia da literacia, do humor ou satisfação dos participantes ou o predomínio de estudos não baseados em encenações sobre o uso de medicamentos) que deverão ser consideradas na apreciação dos resultados e contornadas em estudos futuros.

DESCRIPTORES: Bulas de Medicamentos. Compreensão. Informação de Saúde ao Consumidor. Revisão.

INTRODUCTION

The readability of the package leaflets is an essential issue for the safety and rational use of medicines after they are prescribed or dispensed in pharmacies. Patients may independently consult the package leaflets to clarify their doubts, such as information on medicine administration.[21,22,25]

The inclusion of package leaflets inside all medicine packages is obligatory in the European Union.[a] In accordance with regulations,[29] the package leaflets must be organized in pre-defined sections[b] and written in a clear and comprehensible way.[c]

The European template on the content of the package leaflets is the Quality Review of Documents (QRD).[b] This template was updated several times since the first version was published (1996).[29] According to the

[a] European Parliament and the Council. Directive 2001/83/EC: community code relating to medicinal products for human use. Brussels; 6 Nov 2001 [cited 2013 Aug 12]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
[b] European Medicine Agency. Quality review of documents human product-information annotated template. Version 9. London; 2013 [cited 2013 Oct 13]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jspp
[c] European Medicine Agency. Guideline on the readability of the labelling and package leaflet of medicinal products for human use. London; 2009 [cited 2013 Aug 12]. Available from: http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf

9th version of QRD,[b] the package leaflets should be organized as follows:

1. What X (X = name of the medicine) is and its indicated use;
2. What you need to know before you <take> <use> X;
3. How to <take> <use> X;
4. Possible side effects;
5. How to store X;
6. Contents of the pack and other information.

The results of legibility and usability[c] tests are used to prove the simplicity, clarity, and comprehensibility of the information on the package leaflets for the medicine users.[21,25] The guideline on the readability of the labeling and package leaflet of medicinal products for human use (European commission, 1998) was the first on this issue in Europe and is used by the European Medicine Agency.[c] According to the general principles of these guideline,[a,c] a questionnaire should be administered to at least 20 patients, preferentially from the population for which the medicinal product is intended. Healthcare professionals should not participate in legibility tests[c,d] so as to not bias the results. In contrast, it is advisable that geriatric and less proficient patients participate in these tests because these subjects usually present more difficulties in reading and interpreting documents.[14] The main topics of the package leaflets (indications or contraindications) are commonly selected to be examined.[c] The aims of these tests are to identify problems with the location and comprehension of the information on package leaflets, and if necessary, to optimize the package leaflets[c] and repeat the tests (retests).[21,25] The package leaflets are considered acceptable when the participants obtain at least 90.0% of answers.[d]

Although the medical authorities of each European country evaluate the legibility of package leaflets before their approval,[2] sometimes these documents are not adequately understood [e.g., dosage or adverse drug reactions (ADR)]. This is particularly bad for low-literate patients.[21,25]

The objective of the present study was to review studies on the readability of package leaflets of medicinal products for human use.

METHODS

Systematic review. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria were used to organize the report on the selected studies.[e] The studies were conducted between January 1, 2008 and February 24, 2013 (five years and two months), with the aim of including recent investigations and pharmaceutical regulatory updates.[c]

The study keywords were "readability and package leaflet" or "readability and package insert" separated by the Boolean operator "and". The selection of both designations followed from the fact that the designation "package leaflet" is more common in European countries[c,d] and "package insert" is used outside Europe.[20,f]

The search was performed using the academic search engine, *Biblioteca do Conhecimento Online* (b-on).[g] This tool allows access to thousands of scientific journals and concurrent searches in different databases and bibliographic databases, including BioMed Central,[h] BioOne,[i] Bioline International,[j] Directory of Open Access Journals,[k] Medical Literature Analysis and Retrieval System Online (Medline),[l] United States National Library of Medicine National Institutes of Health (PubMed),[m] Scientific Electronic Library Online (Scielo Global),[n] Elsevier[o] and

[d] The Heads of Medicines Agencies, Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human. Position paper on user testing of package leaflet – consultation with target patient groups. 2011 [cited 2013 Oct 27]. Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_234_2011.pdf

[e] Critérios Prisma - Transparent reporting of systematic reviews and meta-analysis; 2013 [cited 2013 Aug 16]. Available from: http://www.prisma-statement.org/

[f] Australian Governament, Department of Health and Ageing, Therapeutic Good Administration. Mechanisms to maintain the currency of approved Product Information (PI) and Consumer Medicine Information (CMI): public consultation paper. Version 2013 [cited 2013 Aug 12]. Available from: https://www.google.pt/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CDsQFjAB&url=http%3A%2F%2Fwww.tga.gov.au%2Fword%2Fconsult%2Fconsult-opr-currency-pi-cmi-130513.docx&ei=fwdtUvenA_Op7Ab7ooHoDg&usg=AFQjCNHhjdYSrmN2s0muwVNMjwVS6UEu0w&sig2=Jtp7FfAdBJYD2oaORlX4zg&bvm=bv.55123115,d.ZG4&cad=rjtg

[g] B On: Biblioteca do conhecimento online. Lisboa: Fundação para a Computação Nacional; 2013 [cited 2013 Aug 12]. Available from: http://www.b-on.pt/

[h] BMC: BioMed Central the open access publisher; 2014 [cited 2014 Dec 2]. Available from: http://www.biomedcentral.com

[i] BioOne online journals; 2014 [cited 2014 Dec 2]. Available from: http://www.bioone.org/

[j] Bioline International; 2014 [cited 2014 Dec 2]. Available from: http://www.bioline.org.br/

[k] DOAJ: Directory of Open Access Journals; 2014 [cited 2014 Dec 2]. Available from: http://doaj.org/

[l] MEDLINE: Medical Literature Analysis and Retrieval System Online. Bethesda (MD): US National Library of Medicine; [s.d.]. [cited 2014 Jul 28]. Available from: http://www.ncbi.nlm.nih.gov/IEB/ToolBox/SDKDOCS/MEDLINE.HTML

[m] PubMed: the bibliographic database of the United States National Library of Medicine National Institutes of Health [Internet]. Bethesda (MD): National Library of Medicine. [1946] - [cited 2014 Jul 27]. Available from: http://www.ncbi.nlm.nih.gov/pubmed

[n] SciELO: Scientific Electronic Library Online [Internet]. São Paulo (BR): Bireme/OPS/FAPESP/CNPq. [1998]. [cited 2014 Jul 28]. Available from: http://www.scielo.org/php/index.php?lang=en

[o] Elsevier; 2014 [cited 2014 Dec 2]. Available from: http://www.elsevier.com/

SpringerLink.[p] Moreover, two complementary searches were performed. One used PubMed to confirm the existence of additional results, and the other used the Cochrane Collaboration Reviews[q] to confirm the existence of other reviews on this topic, which contributed to validate the interest and relevance of this review. All the review results are properly archived and available for future consultations. The inclusion and exclusion criteria are described in Table 1.

The repeated references were automatically identified using EndNoteWeb (a management references program).[r] The main findings of the selected studies were summarized and organized into a tabular format (objectives, methods, results, and conclusions). The selected studies were divided into the following two categories. The first category comprised exploratory studies (studies with the participation of health professionals or patients), and the second was descriptive studies or studies involving non-enrolling participants (studies using legibility formulas or investigating the linguistic characteristics of texts). In particular, the studies on the readability of ADR were described and analyzed because of the importance of this issue for patient safety.[29] The selected studies were classified as follows:

1. Exploratory studies specifically enrolling health professionals;
2. Exploratory studies enrolling patients (or potential users of medicines), such as studies on comprehension of ADR (readability/usability tests) by patients;
3. Descriptive studies (studies using non-enrolled participants, i.e., all the non-experimental studies) on the readability of package leaflets, including studies that evaluate the number of words, length of phrases, or letter type.

Overall, the selected studies were comparatively analyzed. The main findings, potential limitations, and the opportunity for future work were evaluated and registered.

RESULTS AND DISCUSSION

Twenty-two studies out of the 202 were selected and comprised 16 full papers, three brief communications, and three indexed abstracts. The number of included and excluded studies are presented in Table 2 in addition to different keywords and search tools. The flowchart is organized using the PRISMA[f] criteria, representing the exclusion reasons (Figure). None of the studies on the topics under review was found in the database of Cochrane Collaboration Reviews, confirming the interest in this review.

The main aspects (objectives, methods, results, and conclusions) of the selected studies are summarized in Table 3. The 22 selected studies were distributed as follows: two in Group A (exploratory studies enrolling health professionals), 12 in Group B (exploratory studies enrolling patients or potential patients who will use the medicines), and eight in Group C (descriptive studies).

Overall, few studies on the readability of the package leaflets were identified compared to a search in PubMed using the search term, "patient information", which identified 6,357 search results on October 13, 2013.

Exploratory studies enrolling health professionals, patients or potential users of medicines

In the two exploratory studies (group A),[5,22] wherein healthcare professionals (physicians or pharmacists) participated, it was reported that the healthcare professionals were satisfied with the information in the leaflets. They considered the information in the package leaflets more important than did the actual patients (or potential patients) who required the medicines. In contrast, the patients (or potential patients) who would be using the medicines expressed their preferences for receiving personal explanations on the use of medicines during consultations. One reason for this was due to the high prevalence of technical terms in the package leaflets. Only two studies with healthcare professionals were identified in this revision, although these studies were important to validate the optimized package leaflets.[5,22]

From the twelve exploratory studies with patients (or potential patients) receiving medicines (group B), ten were conducted to evaluate participant comprehension (usability and/or legibility tests,[1,2,6,8,11,12,19,21,25,26] or studies to specifically evaluate participant comprehension of the manner in which ADR were presented.[18,17]

The main problems identified in these 10 studies were patient (or potential patient) comprehension issues as some topics were poorly understood;[2,11,19,25,26] too complex texts, indicating the necessity of optimizing and simplifying the package leaflets;[1,11,12,21] and package leaflets not properly adapted for the low-literate patients, indicating the need to use simpler language.[1,6,8,19]

The majority of the reviewed readability studies used package leaflets of specific medicines, including sildenafil, clozapine, acetaminophen, and diclofenac.[1,6,19,26] It is likely that these package leaflets were selected for

[p] SpringerLink; 2014 [cited 2014 Dec 2]. Available from: http://link.springer.com/
[q] Cochrane collaboration reviews; 2014 [cited 2014 Dec 2]. Available from: http://www.cochrane.org/cochrane-reviews
[r] EndnoteWeb. New York: Thomson Reuters; 2013 [cited 2013 Aug 12]. Available from: https://www.myendnoteweb.com/EndNoteWeb.html?SID=P2g6anKIJyF54XPliP4&returnCode=ROUTER.Success&SrcApp=CR&Init=Yes

Table 1. Inclusion and exclusion criteria of studies on the package leaflets of medicinal products for human use.

Criteria	
Inclusion	Exclusion
Studies or abstracts	Studies or abstracts
Original	Out of the research period
Quantitative	Repeated
Qualitative	Review or opinion
Exploratory	Not directly related with the research topica[a]
Descriptive	Other languages[b]

[a] Studies not specifically related with the package leaflets (e.g., studies on the readability of medicines labels) or medicines (e.g., studies on the readability of the package leaflets of medical devices or information on disease management).
[b] Original documents in languages other than English, Portuguese, Italian, French, or Spanish.

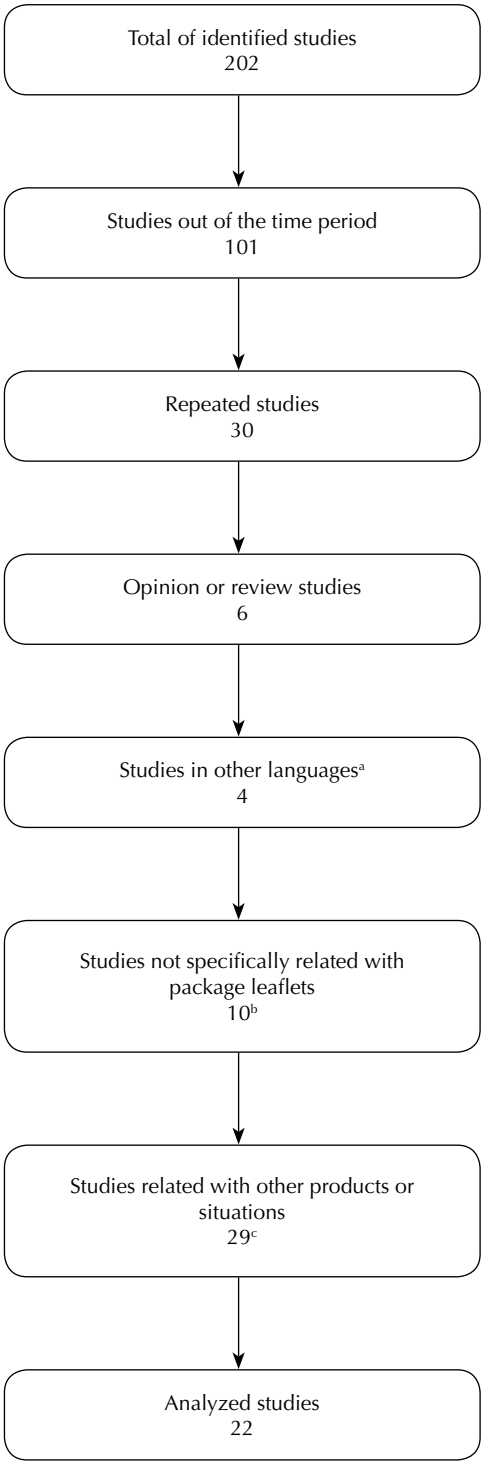
Table 2. Number of studies searched, included and excluded, pear search tools, keywords, and reasons for exclusion; period: January 1, 2008 February 24, 2013.

Search tool	Keywords	Total	Repeated	Excluded/Reasons	Selected[a]
PubMed	"Readability and Package Insert"	17	1	14 10 - out of the period 1 - other language[b] 1 - opinion studies 2 - other topics	2
	"Readability and Package Leaflet"	67	6	58 34 - out of the period 2 - other language 1 - opinion studies 5 - other topics 16 - other products[c]	3
B-on	"Readability and Package Insert"	59	20	32 28 - out of period 1 - other language 3 - other products	7
	"Readability and Package Leaflet"	59	3	46 29 - out of period 4 - opinion studies 3 - other topics 10 - other products[c]	10
Total		202	30	150	22

PubMed: United States National Library of Medicine National Institutes of Health; b-on: *Biblioteca do Conhecimento Online*
[a] Selected studies = Total - Repeated - Excluded.
[b] Original documents in languages other than English, Portuguese, Italian, French, or Spanish.
[c] Studies on the readability of the package leaflets of other products than medications.

the following reasons: the straight therapeutic indices of some medicines such as clozapine,[1] over-the-counter medicines (no prescription necessary), such as diclofenac and acetaminophen, and highly utilized medicines such as acetaminophen.[6,19] The package leaflets of these medicines are more likely to be consulted. Therefore, it is difficult to generalize about or extend conclusions of these studies to the package leaflets of medicines with different active ingredients. The study on the automatic simplification of the technical terms was considered particularly relevant because an automatic methodology was used to simplify diverse package leaflets at the same time. In this study, an informatics tool was used, and the technical terms of the package leaflets were identified. More common and equivalent terms were then found in pre-defined lexical databases and finally, the original terms were automatically replaced by the more common terms.[11]

Diverse limitations were identified in these studies[1,2,6,8,11,12,19,21,25,26] and were categorized as follows: high diversity of methods, limited number of participants, lack of certain assessments (such as the evaluation of participant literacy, humor, cognitive state, and satisfaction), lack of multicenter or longitudinal studies, lack of studies on specific topics such as contra-indications and precautions, study of the package leaflets from a limited number of medicines and active ingredients,[1,6,19,26] and lack of pictograms (useful for low-literate patients) or



[a] Languages: one study in Norwegian and three studies in German.
[b] Studies on the readability of medication informative materials, e.g., external packages or labels.
[c] Studies on the readability of the package leaflets of other products (non-medication), including food, chemicals or herbal products, medical devices, or information on the risk of abortion, clinical trials or disease management.

Figure. Flowchart: exclusion reasons for the researched studies.

other illustrations.[8,24] A few authors reported that the study limitations were contrary to good clinical practices, increasing the difficulty of precisely analyzing the results.

Studies on comprehension of adverse drug reactions

The presentation of ADR was particularly relevant in two studies (group B) because the patient comprehension of ADR strongly depended on the way ADR were presented.[18,17] ADR were described in different manners in these studies. These ADR were described using qualitative descriptors (very common ADR) or quantitative descriptors (adverse reactions with a likelihood of 1.0%-10.0%).[18] Further, it was found that patients preferred numerically expressed ADR (using absolute frequencies)[18,17] and considered the use of fractions (≥ 1/100) to be difficult to understand when the ADR frequency[3,17,18,27] was presented in this manner.

In general, the section of the package leaflets on ADR was compliant with the recommendations of the QRD.[3,17,18,29,b] According to the requirements of the QRD template, ADR are presented in an ordered list of values (from the more to less frequent ADR). For example, a "common" ADR may affect up to 1 in 10 people, and "uncommon" ADR may affect up to 1 in 100 people.[29]

The number of studies specifically concerned with the most appropriate way to present ADR and the number of participants enrolled in these studies were limited.

Descriptive studies

The eight descriptive studies[3,4,13,23,24,27,28,30] (or studies with non-enrolled participants) on the usability of the package leaflets (group C) focused on the following aspects:[3,4,13,23,24,27,28,30] (i) use of legibility formulas, such as Flesch-Kincaid or Fry to calculate values on the association between the linguistic characteristic of texts and the education level of patients (linguistic metrics),[4,23,24,27,28,30] (ii) identification of specific linguistic characteristics (e.g., number of difficult words or phrases) to obtain indirect indicators on the proper readability of texts;[3] and (iii) evaluation of graphical aspects that facilitate the understanding of information (e.g., letter size or presence of illustrations).[24,27,30]

Overall, the application of the descriptive methodologies confirmed a low readability of the package leaflets and the need to simplify the texts. The factors that decrease the readability of the package leaflets were evident in some studies and included the following: too complex texts (e.g., some package leaflets were classified as appropriate for readers with 10 or more years

Table 3. Informative summary of the selected studies on the readability of package leaflets of medicinal products and identified in search tools; period: January 1, 2008–February 24, 2013.

Reference	Objective(s)	Methods	Results	Conclusion
A. Exploratory studies with the participation of health professionals				
Cavaco et al,[5] 2012 (resume)	Optimization of package leaflets	2 groups: potential users and physicians An original and optimized package leaflet (diclofenac) was tested Questionnaires Opinion on technical terms (Likert scale)	42 potential users 42 physicians Satisfaction on the original package leaflet: 0.0% good; 10.0% satisfactory Satisfaction on the technical terms (optimized package leaflet): 20.0% good; 65.0% satisfactory	Lexical modifications produced favorable results
March J et al,[22] 2009	Opinion study	Interviews Flesch formula (25 package leaflets)	Participants: (40) patients, (6) physicians, (11) pharmacists and (13) from associations of patients Health professionals attributed more importance to the package leaflets in comparison to patients More difficult issues: dosage, ADR and contra-indications Flesch index: high	The real needs of health professionals and patients should be considered during the development of package leaflets The patients preferred to receive the direct opinion of health professionals
B. 1. Exploratory studies with the participation of potential users of medicines: studies on patients' comprehension of drug adverse reactions				
Knapp et al,[17] 2010 (brief communication)	Comprehension of ADR	ADR presented in different formats Opinion on the preferred format Imaginary scenario: opinion on the probability of ADR (if taking tamoxifen)	134 participants The absolute frequencies (e.g., 48 persons in each 100) were considered more precise/clear than the interval of frequencies (e.g., affect more than one person in each 10)	The use of absolute frequencies to present ADR demonstrated to be more appropriate
Knapp P et al,[18] 2009	Presentation of ADR	Classification of ADR: using verbal (e.g., rare) or numerical (e.g., 1 in 10) descriptors, or both Imaginary scenario: estimate the risk of 4 ADR and satisfaction (if taking tamoxifen)	187 Participants Absolute frequencies were more favorable	Future studies are advisable
B. 2. Exploratory studies with the participation of users or potential users of medicines: comprehension studies				
Symonds T et al,[26] 2010	Participant comprehension (sildenafil package leaflet)	Two groups of participants: consultation *versus* hypothetical auto-administration Questionnaire Blind study	Participants: 113 healthy men and 70 with health problems (e.g., prostatic hypertrophy) The results between both groups were concordant in more than 73.9%	It may be necessary to optimize the indications

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Shiffman S et al,[25] 2011	Participant comprehension (antidepressant information)	Materials: medication guide and package leaflet Blind study 52 participants	A rare and dangerous ADR was identified by less than 20.0% of the participants	The information was not fully understood
Fuch et al,[12] 2010	Text length (evaluation)	Crossover study: 1,105 participants (first phase), and 1,057 participants (second phase) Tested materials: 5 original package leaflets + 5 optimized package leaflets Questionnaire	The location of information was more difficult in the longer package leaflets Average of words: 2,505 (original) and 2,002 (optimized) The optimized package leaflets contained: less technical words (14 *versus* 86), less abbreviations (4 *versus* 17), and shorter phrases (7 *versus* 29)	The length of the package leaflets was related with participant comprehension The shorter package leaflets (1,500 words) were more adequate
Lee et al,[19] 2012 (abstract)	Legibility tests (comparison)	Two package leaflets: over the counter medicines (acetaminophen) Task: difficult words were underlined Questionnaire: the questions were based on imaginary scenarios and related with the topics of the package leaflets	51 students Better scores (73.0% to 80.0%) on: indications, dosage, pregnancy information, contra-indications, and formulation 118 difficult words	Simplification of the package leaflets (friendlier package leaflets)
Maat HP et al,[21] 2010	Readability (evaluation)	3 original package leaflets + 3 optimized package leaflets (shorter phrases, simple text). Questionnaire	154/164 potential users (original/modified package leaflets) Optimized package leaflets: higher proportion of correct answers and topics located	The use of more narrow criteria to conceive the package leaflets is advisable
Brosnan S et al,[1] 2012	Readability (evaluation)	Patients with a prescription of clozapine A validated tool was used to evaluate patients' literacy Optimized package leaflet: shorter phrases Questionnaire on comprehension	40 patients Literacy: 29 (72.5%) adequate, 11 low Score of questionnaire: 72.5% (original package leaflet), 95.0% (optimized package leaflet)	It is important to consider patients' literacy during the optimization of package leaflets
Cavaco A et al,[6] 2012 (Brief communication)	Literacy and readability	Clients of community pharmacies A validated tool was used to evaluate participant literacy Satisfaction with the readability of a diclofenac package leaflet (Likert scale)	53 participants (40.0% higher education, 80.0% adequate literacy) The average satisfaction was scored slightly below the neutrality Less favorable issues: letter size, medical technical terms, and abbreviations	The readability issues were not related with the literacy level

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Calamusa A et al,[2] 2012	Quantifying knowledge	Questionnaire (drug store in large shopping areas) Topics: medicine use and specific terminology	1,206 adults 42.0% participants mistook contraindications for ADR Lack of information on the long-term use of: laxatives (14.0%) or nasal decongestants (20.0%)	Advice on the use of medicines is recommended
Dowse R et al,[8] 2011	Participant comprehension	Low-literate participants Package leaflet containing pictograms (anti-retroviral) Interview: locate and explain the information, and give opinion on the use of pictograms	39 participants Average (comprehension): 60.0% The zones of text with pictograms were better understood All participants agreed with the use of pictograms	It is important to consider patient literacy in the development of package leaflets The use of pictograms is likely to increase the intelligibility of package leaflets
Franck J et al,[11] 2011	Participant comprehension	2 package leaflets (oxazepam and tetracycline) An informatics tool was used to optimize the package leaflets (brief explanation on medical terms) Legibility tests (in accordance to the guideline of European Medicine Agency)	Participants: 10/20 (original/ optimized package leaflets) Participant literacy: homogeneous Optimized package leaflets: more favorable results	The time and cost to optimize the package leaflets was reduced in consequence of using an informatics methodology
C. Descriptive studies: evaluation of the linguistic characteristics				
Weiss SM et al,[28] 2010	Adequacy of texts	Informative materials: approved/not approved by Food and Drug Administration Formula of Simple Measure of Gobbledygook (SMOG)	Index of SMOG: above the recommended	Simplification of the package leaflets, especially for the low educated patients
Fuch J et al,[13] 2010	Information (characterization)	271 package leaflets Quantification: number of words/ difficult words Other topics identified: maximum daily dose, ADR, among other	Distribution of the information in the package leaflets: 29.5% maximum daily dosage; 54.6% ADR, and 24.2% frequency of ADR The more recent package leaflets were lengthier and comprised a higher proportion of difficult words	Simplification of the package leaflets, such as useful information to patients
Knapp P et al,[3] 2008 (brief communication)	Presentation of ADR	50 Package leaflets Presentation of ADR: characterization and evaluation	20 (40.0%) of the package leaflets gave no indication of the likelihood of the ADR 26 (42.0%) package leaflets included verbal descriptors, such as the general designation "common" 4 (8.0%) included data of frequency	In the majority of the cases ADR were not adequately presented

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Pinero-Lopez MA et al,[23] 2011 (abstract)	Evaluation of text-readability	Package leaflets of biopharmaceutical medicines Formulas: SMOG and Flesch	40 package leaflets Readability index: low (both formulas) Most difficult section: ADR	Simplification of the package leaflets
Roskos SE et al,[24] 2008	Evaluation of text-readability	7 package leaflets of nasal steroids Formula of Fry The size of letter and illustrations size were evaluated	On average, the package leaflets were classified as appropriate to people with seven years of schooling (instead of the five years recommended) Letter size: 9 instead of 11 (or the minimum recommended size) Only three pictures in the package leaflets	Readability problems were identified
Wallace et al,[27] 2007	Adequacy of texts	83 sample of tablets + package leaflets (hospital) Formula of Fry Letter size	Package leaflets: only in 19 samples The package leaflets were classified as appropriate to people with 10 years of schooling (formula values)	Ideally, samples should contain package leaflets Simplification of the package leaflets
Zite NB et al,[30] 2008	Characteristics of texts	8 package leaflets (contraceptive). Formula of Gobbledygook "User-Friendliness Toll" to evaluate: layout, graphical aspects and clarity of information	The package leaflets were classified as appropriate to people with 10 years of schooling (formula values) It was found dosage issues and different explanations on the ideal contraceptive effect	Simplification of the package leaflets (review of texts)
Cavaco A et al,[4] 2010	Evaluation of text-readability	4 package leaflets Translation: Portuguese to English Formulas of SMOG and Flesch-kincaid (English translations)	The package leaflets were classified as appropriate to people with 10 years of schooling (formula values) Correlation of Spearman between the results: high	Simplification of the package leaflets for less-educated people (adjustment/ adaptation)

ADR: Adverse drug reactions; SMOG: Formula of Simple Measure of Gobbledygook

of education, instead of the five years recommended by Food and Drug Administration);[s] omission of relevant technical information (e.g., maximum daily dose,[3,4,13,23,24,27,28,30] extensive use of technical words[13] or small letters (e.g., letters with a font size of < 11;[24,27] and lack of illustrations.[24,30]

We believe that the lack of readability formulae or other alternative linguistic metrics to evaluate texts specifically written in Portuguese[7,9,10,15,16] constitutes a limitation. The legibility concepts developed in the 1920s and have been continued by writers such as Rudolf Flesch,[10] George Klare,[16] Edgar Dale, and Jeanne Chall.[7] The Gunning formula (1935)[15] was one of the first, and according to the equation of this formula (suitable for English texts), the education level is equal to 0.4*(average size of phrases in number of words + the number of words with more than two syllables per 100 words).[9] There are currently several legibility formulas for diverse languages, such as Spanish, French, German, Swedish, Russian, Hebrew, Hindi,

[s] Food and Drug Administration: Guidance for Industry – Label comprehension studies for Nonprescription Drug Products; 2014 [cited 2010 Dec 2]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm143834.pdf

Chinese, Vietnamese, and Korean.[9] However, it is not known if legibility formulas specifically developed for the Portuguese language exist. Similar to other languages, Portuguese presents a specific combination of linguistic characteristics; thus, the development of legibility formulae specifically developed to evaluate the readability of Portuguese texts is recommended.[4]

In some studies, it was not possible to cross-check the results of different formulae (double verification)[24,28,30] due to the fact that only one legibility formula was used.

Summary of the methodological limitations

In the studies of this review, the principal limitations identified are listed:

1. The inclusion of a limited number of patients or health professional in the readability and/or usability studies, particularly in the non-confirmatory studies;[1,5,6,8,11,19,21,22,25,26]

2. The lack of certain evaluations before the study, such as the evaluation of the participants' cognitive state, humor, satisfaction in participating in the test or opinion on the use of medicines and their package leaflets. These factors are likely to influence the interpretation of the results (interpretation bias);[8]

3. In majority of cases, participant literacy was also not evaluated, which probably influenced the accuracy of the study conclusions;[14]

4. The non-use of the original packages of medicines or the absence of questions based on imaginary scenarios in several readability and/or usability tests, probably also influenced the accuracy of data collection;[21]

5. The illustrations were scarcely used, namely pictograms,[10] despite these graphic elements favoring the readability;

6. The selection of packages leaflets based on the composition of the medicines, (type of active ingredients)[1,6,19,26] may influence their selection (selection bias) because in general, the package leaflets with the worst linguistic characteristics were not selected, such as the longer package leaflets or the those containing more sentences per paragraph, abbreviations, or acronyms;

7. Few studies on patient comprehension of ADR[3,17,26] and absence of studies on patient comprehension of specific topics, such as precautions, interactions, and contraindications;

8. The nonexistence of multicenter studies to study intra- and intercultural differences, such as dialectal differences;

9. The absence of longitudinal studies to investigate possible alterations over time, such as those caused by social changes, alterations on the pharmaceutical regulation or the appearance of new therapeutics;

10. Studies using only one legibility formula, which does not allow the comparison of different metrics. However, the results obtained through the application of legibility formulas are highly correlated according to some studies;[9]

11. The lack of legibility formulae for Portuguese to calculate indicators on the simplicity of texts, similarly to the legibility formulas of other languages, such as English (e.g., Flesch formula).

Because of these methodological limitations, it is possible that the studied package leaflets were not accurately evaluated.

CONCLUSIONS

The studies on the readability of the package leaflets should be based on technical principles and be highly suitable with high quality scientific standards. Several points are strongly recommended for improving and standardizing the readability of package leaflets. These include minimizing or avoiding the previously discussed limitations, using larger and more varied samples of package leaflets, enrolling more participants, and development of new metrics and legibility formulas for specific languages (e.g., Portuguese).

In this review, diverse factors related with the readability of the package leaflets were highlighted (e.g., clear information, simple terms, and package leaflets with a proper design. The main methods for ensuring the intelligibility and comprehension of the package leaflets were the usability tests and the application of formulae and/or metrics to their texts.

The encountered readability/usability tests rely on the involvement of patients using the medication to test and confirm the readability of the informative materials. Ideally, these tests should also include patients with low literacy levels and health professionals to ensure the collection of reliable and efficient results.

The diverse methodological limitations identified should be avoided in future studies and considered in the assessment of results.

In general, the investigations on the readability of the package leaflets and their methods need more scientific contributions to assure the accuracy, reliability, and appropriateness of results in the social context and language of each country.

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