DOI: 10.1590/1413-81232017228.05762017

Impact of interventions to promote the use of generic drugs: a systematic review

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Abstract *The need to increase access to medicines, coupled with the limited acceptance of generics has sparked the search for effective interventions to promote it. This systematic review aimed to conduct a survey on interventions to promote the use of generic drugs and its impact. Randomized clinical trials, non-randomized controlled trials, controlled before-after studies and interrupted time series were included. The analysis of the impact of interventions and quality of evidence followed Cochrane's guidelines. Impact of interventions was rated from "very large" to "very small" and the quality of evidence was rated from "high" to "very low". Seventeen papers addressing prescribers, pharmacists and users were selected. There were educational, financial incentives and use of electronic prescription and managerial interventions. Interventions applied to prescribers had little to medium impact, with very low-to-low quality evidence. Interventions applied to pharmacists had small impact with very low quality evidence. Interventions applied to users had medium and large impact with very low-to-low quality evidence. Further studies with good quality addressing interventions are required.*

Key words *Systematic review, Generic drugs, Interventions, Medicines replacement*

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Introduction

Increasing drug expenditure is a concern of several countries[1-4]. Thus, a number of measures such as interventions and campaigns are established to address reduction of this spending, which include the promotion of generic drugs[3,5] have been increasingly used to expand access to medicines[5].

The share of generic drugs in the market differs between countries. In the United States and Germany, for example, this share is 60% in volume, while in others, such as Spain, France and Brazil, generic drugs hold between 27% and 42% market share[6,7].

The main reasons for the low use of generic drugs are the lack of prescription by generic name[8] and negative perception about them[9]. Lack of consumer knowledge is also a hurdle to its use[10]. A frequent problem is the polysemy of the term "generic drug" due to its different definitions according to each national legislation[11].

However, most users seem to accept replacement with generic drugs[12]. In recent years, trust and use of generics has increased, especially in developed countries, due to educational efforts, increased monitoring of good manufacturing practices, ensuring quality of medication and the greater communication of users with their caregivers[13,14].

Strategies to encourage the consumption of generic drugs are directed at users, prescribers or pharmacists[15] and have been adopted to increase their acceptance and use[1,8,14]. These strategies aim to increase users' and/or prescribers' confidence and knowledge about these drugs[14], since some of these stakeholders are still skeptical about the bioequivalence tests performed.

Most of the interventions observed in the literature focus on the physician's behavioral change regarding its prescription[16,17] to improve its quality and promote the rational use of medicines[18].

Dunne & Dunne[19] conducted a review of observational and qualitative studies on the knowledge, acceptance and use of generic drugs from the perspective of physicians, pharmacists and consumers, showing the importance of information and knowledge about the equivalence of generic drugs, but without evaluating the interventions used to improve their prospects and broaden their use. Another narrative review of literature on generic drugs was performed by Babar et al.[1], which aimed to describe the strategies and interventions to promote the acceptance of generic drugs, which led to the identification of different types of interventions to increase the use of these drugs, but this study does not show an evaluation of the impact of the observed interventions. Moe-Byrne et al.[20] reviewed behavioral change interventions to promote the prescription of generic drugs addressing prescriptions.

No revisions were found that had evaluated interventions that aimed to increase the use of generic drugs focused on the three stakeholders (prescriber, user and pharmacists) involved in the generic drug choice. In addition, the aforementioned reviews do not summarize the impact and quality of interventions, which could help the decision-making of managers, aiming at the expansion of generic drugs. Thus, this study aimed to carry out a systematic review of literature on interventions geared to the promotion of the use of generic drugs in order to evaluate their impact.

Methods

Search strategy

Review of literature in the PubMed / Medline, Web of Science and Lilacs databases using the following keywords to identify generic drugs: *"generics"; "generic alternatives"; "generic drug"; "drugs, generic"; "generic medicine"; "generic/therapeutic substitution"; "medication substitution"; "generic substitution"; "generic prescription"; "generic dispensing ratio"; "generic dispensing rate"; "generic drugs"; "drug utilization"; "drug substitution"; "nonproprietary drugs"; "non-proprietary drugs"; "generic medication"; "generic medications"; "generic name"; "generic names"*.

The following terms were used to characterize the studies as interventions: "intervention"; "educational intervention"; "multiple interventions"; "administrative interventions"; "randomized clinical trials"; "non-randomized controlled trials"; "controlled before-after"; "interrupted times series"; "repeated measures studies"; "interventions"; "pre-post study"; "pre and post"; "before and after"; "controlled trial"; "clinical trial"; "randomized, controlled trial"; "randomized controlled trial".

Search was performed on February 23, 2016. The strategy included the availability of descriptors / keywords, located in all fields of the paper, without language restriction or year of publication. Papers were searched in open access or in the CAPES journals database, with request to the contact author when not available.

Ciência & Saúde Coletiva, 22(8):2627-2644, 2017

Inclusion criteria

The guidelines that follow the taxonomy and criteria proposed by Cochrane's Effective Practice and Organization of Care (EPOC)[21] were used as inclusion criteria in the study: randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), controlled before-after trials (CBA), interrupted time series (ITS) and repeated measures studies (RMS). The target populations of interventions were prescribers, pharmacists and users, with no restriction as to the sample selection location (setting or context).

Exclusion criterion

Papers with clinical trial protocols that did not contain results, papers with different designs than those suggested by Cochrane's EPOC, before-after studies with no control group, interventions that did not promote the generic drug or that considered the entry of the generic drug in the market as intervention and those whose sum of the evidence quality assessments were left with an overall evidence quality score equal to zero were excluded.

Selection and Extraction Process

The search key was established by two co-authors, and search was conducted in a single day by only one of them. All data selection and extraction was performed by two independent reviewers (MG and MS), with the participation of the other authors in conflicting cases. A database was built in Excel© with papers retrieved to carry out the selection and extraction process. After exclusion of duplicate titles, titles and abstracts were read, excluding those that did not comply with the inclusion criteria.

After reading titles, those who referred to change in prescription, dispensation, perception, acceptance, replacement or use of generic drugs were selected. Subsequently, while reading the abstracts, those whose designs were eligible, original papers and those evaluating interventions of interest were maintained. Figure 1 shows the systematic review flowchart.

Interventions of Interest

Regarding interventions of interest, we considered all those that could increase the use, prescription and/or dispensing of generic drugs. Based on the proposal of Babar et al.[1], interventions were classified as: (a) educational, (b) financial incentive, (c) electronic prescription, (d) managerial. When classification categories were overlapped in the same intervention, they were classified under the preponderant category, defined by consensus.

Studies description

The prescriber, pharmacist and/or user's behavioral change was considered as an outcome. Prescribers were screened for changes in the prescription of generic and reference drugs, pharmacists on the replacement of reference medicines with generic drugs, and users on the change in the relative use of generic drugs over reference medicines and on the replacement of reference medicines with generic drugs.

Studies were described according to the following aspects: year of publication, country of performance, design, intervention type, intervention's target population, intervention period and outcome measures (Chart 1).

Evidence quality evaluation

The evidence quality score was evaluated by consensus among authors, using the grades of evidence as per the Working Group Grades of Evidence (GRADE), a tool suggested by Cochrane[21,22], which assesses design, risk of bias, inconsistency, indirect evidence, inaccuracy and conflict of interest. (Chart 2). Each analyzed characteristic receives a score according to the quality of papers. The sum of scores from each evaluation generates the evidence quality score (classified as very low, low, moderate or high), which was provided to the study group of each intervention for each outcome (Chart 3).

Designs scored from one to four, considering the randomized trials as those with the highest scores (4), and the interrupted time series and repeated measures as studies with the lowest scores (2 or 1).

A realm-based tool was used[21-24] to assess the risk of bias, where a critical evaluation is performed separately for different aspects of the risk of bias of each design. Nine realms were assessed for RCT, NRCT and CBA, namely: (1) generation of random sequence; (2) concealment of allocation; (3) measure of similar outcome in the intervention and control group; (4) baseline study results similar between control and intervention; (5) blinding participants and professionals regarding the allocation of intervention;

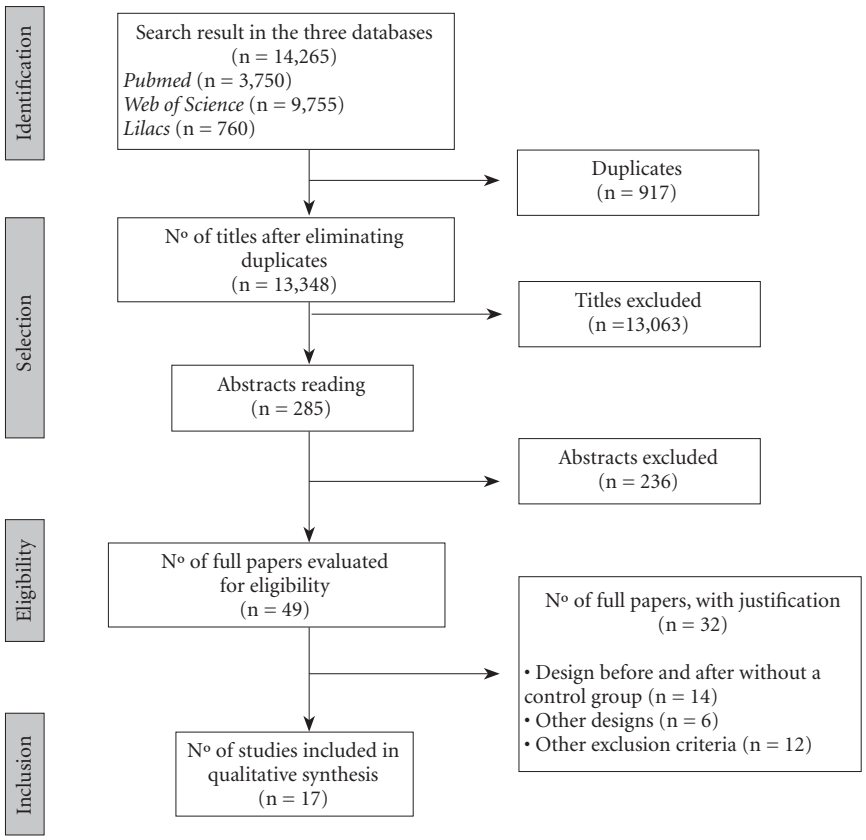

Figure 1. Flowchart of the process of identification and selection of papers on interventions that promote the use of generic drugs.

(6) blinding outcome evaluators; (7) incomplete outcomes; (8) reporting of selective results; (9) other risks of bias. Seven realms were assessed to evaluate the ITS design,: (1) independent observation in relation to other changes; (2) intervention effect type; (3) probability of intervention affecting data collection; (4) blinding participants and professionals regarding the allocation of intervention; (5) incomplete outcomes; (6) reporting of selective results; (7) other risks of bias. Three possibilities of classification (low, high or uncertain) were considered for each realm of risk of bias analyzed (Table 1). After this realm evaluation, the study group of each intervention, separated by outcomes, received a single classification regarding the severity of the risk of bias[24].

The inconsistency evaluation refers to the analysis of the meaning of the results of different studies[27]. The evaluation of indirect evidence takes into account studies' comparability regarding population, intervention and outcome measures[28]. The assessment of inaccuracy considers the measures of outcomes studied and their confidence intervals[29]. Finally, conflict of interest was assessed.

Assessment of risk of bias, inconsistency, indirect evidence and inaccuracy were scored as Not serious (0), Serious (-1) and Very serious (-2).

The summary of the impact of interventions to promote the use of generic drugs was performed according to the Cochrane proposal[34], where authors, in a consensus, heuristically classified the effects of interventions as very large, large, medium, small or very small, taking into consideration their magnitude.

Studies that showed, in the comparison between intervention and control or in the comparison between before-after in the measurement of

Chart 1. Description of the selected articles, according to the types of interventions that promote the use of generic drugs.

Reference; Country	Setting / Specific context	Intervention; Intervention's period of implementation	Sample	Outcome
Educational interventions affecting generic prescription				
NRCT				
Wensing et al., 2009[18]; Germany	PHC clinics	Periodic meetings with physicians to inform generic prescription rates and clarify doubts; 2001 to 2003.	3,180 physicians (Intervention 1,090; Control 2,090).	Compared to the control group, the intervention group increased, on average, the prescription of all drugs with the possibility of prescribing the generic in 0.75% CI 95% 0.40 - 1.10].
Niquille et al., 2010[25]; Switzerland	PHC clinics	Continuing education on practical norms and feedback on prescriptions at meetings moderated by trained pharmacists	24 physicians, 6 pharmacists	The increase of each class of drug in the period was as follows: Beta-blockers (I-24.9 C-21.3); Calcium channel blockers (I- 42.1 C-43.6); Antihypertensive agents (I-7.44 C-13.6); Diuretics (I-32.2 C-37.8); Lipid-lowering agents (I-45.9 C-39.2). It does not show global data on generics.
Rausell et al., 2005[17]; Spain	Hospital	Monthly individual reports of revenue reviews. Intervention was implemented in June 2003; monitoring occurred at 4-6 and 10-12 months following the intervention;	94 physicians from 16 services	There was no significant difference in the proportion of generics in the pre-intervention period p = 0.284. After 4-6 months, means were as follows: control group, 1.81% (95% CI 1.08-2.54), and intervention group, 3.13% (95% CI 1.79 - 4.47); p = 0.041. After 10-12 months, the control group showed a mean of 2.22% (95% CI 1.56-2.87) and the intervention group, 4.01% (95% CI 2.28-5.73); p = 0.025. Significant difference between groups, maintained in the two post-intervention periods.
Walker & Mathers, 2002[26]; United Kingdom	PHC clinics	Pharmaceutical counseling, practical feedback, evaluative meetings, written information. Feb to May 1998.	Intervention: 36 physicians from 9 clinics; Control: 44 physicians from 9 clinics	Median change of 5.37% (IQR 2.56-6.32) prescriptions in the intervention group and 1.61% (IQR 1.37-4.27) prescriptions in the control group; p = 0.17.
Calvo Alcántara & Inesta Garcia, 1999[3]; Spain	PHC clinics	Educational sessions on generics (advantages, drawbacks ...), list of selected generic drugs and reports on generic prescription; Jan 1993 to Sep 1993 (pre) Jan 1994 to Sep 1994 (During / post)	Intervention: 24 physicians from 5 clinics Control: 24 physicians from 5 clinics	Pre-intervention: the mean of generic drugs in the control area was 0.87 generic items / 100 thousand inhabitants (SD 0.29) and 1.07 / 100 thousand inhabitants in intervention (SD 0.51); p = 0.0923. Post-intervention: the mean of generic drugs prescribed in the control area was 0.98 / 100 thousand inhabitants (SD 0.37) and 1.61 / 100 thousand inhabitants in intervention (SD 0.81); p=0.0012.

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post-intervention outcomes, differences smaller than 5 p.p. were of very small impact; greater than or equal to 5 and less than 10 p.p., small impact; greater than or equal to 10 and less than 15 p.p., average impact; greater than or equal to 15 and less than 20 p.p., large impact; and greater than or equal to 20 p.p., very large impact. (Chart 3)

The mathematical summary of findings was not performed because studies showed outcomes with different measures.

Chart 1. continuation

Reference; Country	Setting / Specific context	Intervention; Intervention's period of implementation	Sample	Outcome
CBA				
Wensing et al., 2004[30]; Germany	PHC clinics	Feedback on prescriptions and intensive program of educational sessions (n = 11) for small groups of prescribers; Apr to Jun 1998	177 prescribers	Baseline: intervention group 68.3% of the prescriptions were generic and 67.4% in the control group. Post intervention: 71.1% of the prescriptions were generic in the intervention group and 68.4% in the control group. Effect of intervention was OR 1.10 (95% CI 1.08-1.13).
Sicras Mainar & Palaez de Lono, 2005[31]; Spain	Geriatric centers	Letter of presentation, informative interview, monitoring of prescriptions with return of prescription information to physicians; Jan 2002 to Dec 2003	Intervention: 32 geriatric residences (21 and 11 in 2002 and 2003, respectively); Control: 161 geriatric residences (75 and 86 in 2002 and 2003, respectively).	Generic prescription increased in the intervention group from 8.1% to 18.4% and from 8.3% to 14.6 in the control group. Year-on-year growth of 127.2% for the intervention group and 75.9% for the control group (p <0.001)
ITS				
[d]Lopez-Picazo Ferrer et al., 2002[32]; Spain	PHC clinics	Monthly report on the pattern of generic prescription; half-yearly letters updating the printed list of generic drugs; dissemination and discussion sessions on the results achieved; Oct 1998 to Mar 2000.	339 physicians from 45 teams	Prescription of generics increased from 2.79% in the pre-intervention period to 17.63% in post-intervention. The absolute increase was 14.84% and the relative increase was 15.27%. Before the intervention, mean of prescriptions by generic name was 3.12%; during the intervention, it was 11.9%; and after the intervention, it increased to 20.25%.
Educational interventions affecting the pharmacist in the replacement of reference medicines with generic drugs				
RCT				
Knowlton & Knapp, 1994[33]; USA	Community pharmacies	Workshop for pharmacists to intervene in the choice between branded or generic medicines; Apr to Dec 1991	Intervention: 9 pharmacists; Control: 9 pharmacists; Comparison: 9 pharmacists	The average replacement rate of generic drugs in the intervention group pharmacies was 6.34% higher compared to control pharmacies (35.83% vs. 29.45%, p <0.05).
Educational interventions affecting the prescription of reference drugs				
CBA				
Mastura & Teng, 2008[16]; Malaysia	PHC clinics	Meetings for detailed information on prescription by generic name; March to Apr. 2004	Two clinics; 9 offices (5 intervention and 4 control); 3,371 prescriptions	Significant reduction of prescription of drugs by reference name comparing the pre- and post-intervention phases. Reduction from 33.9% to 19.0%, representing a 44% reduction (post-intervention RR of 0.56; 95% CI 0.48-0.66).

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Results

There were 14,265 references (9,755 in Web of Science, 3,750 in PubMed / Medline and 760 in Lilacs). Of these, 917 were excluded due to duplication, resulting in 13,348 references for titles reading. Following this stage, the two reviewers read 285 abstracts. Of these, 49 references were

Chart 1. continuation

Reference; Country	Setting / Specific context	Intervention; Intervention's period of implementation	Sample	Outcome
Educational interventions affecting user's replacement of reference medicines with generic drugs				
NRCT				
Sedjo & Cox, 2009[35]; USA	Health plan	Receiving messages encouraging treatment adherence and increasing awareness on the low cost of the generic alternative; 2007	Intervention: 904 plan members; Control: 1,409 members	Those who received educational intervention were more likely to replace with the lower cost generic antihypertensive (ACEI) (ORadj = 29.82, 95% CI 4.41-201.93) and there was no difference for users of antidepressants and lipid-lowering agents.
Financial incentives affecting generic prescription				
RCT				
Bhargava et al., 2010[36]; USA	PHC clinics	Intervention: Receipt of generic drug voucher + folder with generic drug information; Control: folder only; Jul. 2007 to Mar. 2008	21 clinics (10 intervention x 11 control) participated	The generic dispensing rate for all drugs increased by 7.4 percentage points (p.p.) in the intervention group (53.4% to 60.8%) and 6.2 percentage points in the control group (55.9% to 62.1%). The estimated effect of the voucher is an increased generic dispensing rate of 1.77 p.p. (p = 0.047)
ITS				
[d]Lopez-Picazo Ferrer et al., 2002[32]; Spain	PHC clinics	Monthly report on the pattern of generic prescription; half-yearly letters updating the printed list of generic drugs; dissemination and discussion sessions on the results achieved; and financial incentive for each prescriber to achieve those goals; Oct 1998 to Mar 2000.	339 physicians from 45 teams	Prescription of generics increased from 2.79% in the pre-intervention period to 17.63% in post-intervention. Absolute increase was 14.84% and the relative increase was 15.27%. Prior to intervention, the mean of prescriptions by generic name was 3.12%; during intervention, 11.9% and after the intervention, 20.25%.
CBA				
Scott et al., 2007[37]; USA	PHC clinics	Implementation of automated generic sample supply system supplemented by detailed information (on co-payment, evidence-based information on replacement, chemical equivalence and patent expiry); 2003 to 2006.	2005: 64 clinics and 301 prescribers; 2006: 168 clinics and 631 prescribers	Baseline Measures: dispensed Generic drug rate (DGR) was 47.8% in both groups. After the first year, DGR had an absolute increase of 7.5 p.p. (from 47.8 to 55.3%) in the intervention group, and 6.3 p.p. (47.8% to 54.1%) in the control group. The absolute difference between the participant and nonparticipant groups in the first year of follow-up was 1.2 p.p. In the second year, the difference fell to 0.8 p.p. (59.9% for the intervention group and 59.1% in the control group).

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selected for full-text reading. After evaluation of full-text papers, 32 were excluded (Figure 1). The 17 articles selected were published between 1993 and 2010, fourteen in English and three in

Chart 1. continuation

Reference; Country	Setting / Specific context	Intervention; Intervention's period of implementation	Sample	Outcome
Financial incentives affecting user's use of generics over reference drugs				
CBA				
Dunn et al., 2006[4]; USA	Health Plan's Mental Health Clinics	Introduction of a "Generic Start! Program" with financial incentives to generics in the "3-tiered" co-payment system; Jan. 2004 to Dec 2005	Intervention: 440 thousand HMO members; Control: 500 thousand HMO members	Prescription of generics increased 20 p.p. (32.5% to 52.5%) in the intervention group and 7.4 p.p. in the control group (24.9 to 32.3%) between 2004 and 2005, with a relative increase of 61.5% in the intervention group and 29.7% in the control group.
Electronic prescription affecting user's use of generics over reference drugs				
CBA				
Fischer et al., 2014[38]; USA	University Medica Center	Electronic prescription that brings the generic to prominence; Oct 2003 to Mar 2004	Intervention: 35,651 physicians; Control: 1,198 physicians	Generic equal to "Tiers 1". Baseline: the proportion of generic prescriptions was 53.2% in the intervention group and 54.8% in the control group. After the intervention: 61.4% of electronic prescriptions were generic, representing a 6.6% increase in the generic prescription rate (95% CI 5.9%-7.3%) compared to a 2.6% increase (95% CI 2.5-2.7%) in the control group.
ITS				
Stenner et al., 2010[39]; USA	Hospital	Electronic prescription that brings the generic to prominence; Jul 2005 to Sep 2008.	Over de 1.1 million electronic prescriptions	The proportion of generic drugs increased after the intervention, from 32.1% to 54.2% (an increase of 22.1% 95% CI 21.9%-22.3%). In the control group, the proportion of generic prescriptions was 29.3%, 31.4% and 37.4% in the pre-intervention, post-intervention and final study periods, respectively).
Managerial Reform affecting user's use of generics over reference drugs				
CBA				
Bradlow & Coulter, 1993[40]; United Kingdom	Medical clinics	Reform in the NHS (introduction of budget ceiling for prescribers); 1990/1 - phase 1; 1991/2 - phase 2	Intervention: fixed-budget clinics; Control: clinics without a fixed budget.	The percentage of generic drugs prescribed in the two phases of the study Phase 1 - with a dispensing budget ceiling: 26.9%. Without a non-dispensing budget ceiling: 46.5%. Phase 2 - Fixed dispensing budget - 34.5% [increased 7.6% (95% CI 7.2 - 8.0)] and control - 46.6% [increased 0.1% (95% CI 0.2-0.4)].

[a] Randomized controlled trials (RCTs), non-randomized controlled trials (NRCT), controlled before-and-after (CBA), interrupted time series (ITS) and repeated measures studies (RMS); [d] Lopez-Picazo Ferrer et al.[34] appears twice in the table because it shows two interventions: educational and financial incentive.

Chart 2. Assessment of the quality of evidence of interventions geared to the promotion of generic drugs.

Educational Intervention						
Studies' population	Physicians and users in general, members of the same health plan					
Context	High- and upper-middle income countries; High HDI countries					
Intervention	Educational intervention focusing on prescriber, pharmacists or users					
Comparison	Lack of educational intervention					
Outcome	**Number of studies**	**Quality of evidence assessment**				
		Risk of bias	**Inconsistency**	**Indirect evidence**	**Inaccuracy**	**Conflict of Interest**
Change in prescriber's behavior						
Prescription of generic drugs	8 (4 NRCT[1], 3 CBA[2], 1 ITS[3])	Serious	Not serious	Serious	Not serious	Not serious
Prescription of reference medicine	1 (CBA[4])	Serious	Not serious	Not serious	Not serious	Not serious
Change in pharmacist's behavior						
Replacement of the reference medicine with generic drug	1 (RCT[5])	Not serious	Not serious	Not serious	Not serious	Serious
Change in user's behavior						
Replacement of the reference medicine with generic drug	1 (NRCT[6])	Serious	Not serious	Not serious	Serious	Not serious
(1) Wensing et al.2009, Niquille et al. 2010, Rausell Rausell et al. 2005; Calvo Alcântara et al.1999; (2) Wensing et al. 2004, Walker et al.2002, Sicras Mainar et al. 2005; (3) Lopez-Picazo Ferrer et al. 2002; (4) Mastura et al.2008; (5) Knowlton et al.1994; (6) Sedjo et al. 2009						
Financial Incentive						
Studies' population	Users on antihypertensive treatment					
Context	High income country; High HDI country (EU)					
Intervention	Change or introduction in the financial incentive					
Comparison	Free first treatment or payment at market value					
Outcome	**Number of studies**	**Quality of evidence assessment**				
		Risk of bias	**Inconsistency**	**Indirect evidence**	**Inaccuracy**	**Conflict of Interest**
Change in prescriber's behavior						
Prescription of generic drugs	3 (1 RCT[7], 1 CBA[8], 1 ITS[9])	Not serious	Not serious	Not serious	Not serious	Not serious
Change in user's behavior						
Relative use of generic drug compared to reference medicine	1 (1 ITS[10])	Not serious	Not serious	Serious	Not serious	Not serious
(7) Bhargava et al. 2010; (8) Scott et al. 2007; (9) Lopez-Picazo Ferrer et al. 2002; (10) Dunn et al. 2006						

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Spanish. All used secondary data from prescription records and drug sales. A study was conducted in a high-middle-income country[16] and 16 in high-income countries[3,17,25,26,30-32,35-42]. The selected designs were two RCTs, five NRCTs, seven CBAs and three ITS. The interventions were found to be educational[3,16-18,25,26,30-32,35], of financial incentive[4,32,36,37], electronic prescription[38,39] and managerial[40]. The main characteristics of the studies are summarized in Chart 1.

Table 1 describes the assessment of the risk of bias of the selected studies, accord-

Chart 2. continuation

Electronic Prescription						
Studies' population	Physicians					
Context	High income country; Very high HDI country					
Intervention	Introduction of electronic prescription					
Comparison	Lack of electronic prescription					
Outcome	**Number of studies**	**Quality of evidence assessment**				
		Risk of bias	**Inconsistency**	**Indirect evidence**	**Inaccuracy**	**Conflict of Interest**
Change in prescriber's behavior						
Prescription of generic drugs	2 (1 CBA[11], 1 ITS[12])	Not serious	Not serious	Serious	Not serious	Not serious
(11) Fischer et al. 2014; (12) Stenner et al. 2010						
Management (reform of the United Kingdom's National Health System)						
Studies' population	Physicians					
Context	High income country; Very high HDI country					
Intervention	Introduction of Fundholding (budget ceiling managed by physician)					
Comparison	Lack of Fundholding					
Outcome	**Number of studies**	**Quality of evidence assessment**				
		Risk of bias	**Inconsistency**	**Indirect evidence**	**Inaccuracy**	**Conflict of Interest**
Change in prescriber's behavior						
Prescription of generic drugs	1 CBA[13]	Serious	Not serious	Not serious	Not serious	Not serious
(13) Bradlow et al. 1993						

ing to realms evaluated. Most studies have a high risk of bias because they are not randomized[3,4,16-18,25,26,30-32,35,37-40,42] and do not show information about blinding of the intervention group (realm five RCT, NRCT and CBA), classifying as uncertain risk of bias in this area. All of them evidence a high risk of other biases, mainly for selection bias (realm nine for RCT, NRCT and CBA and seven for ITS) and low risk of bias in the realm of blinding outcome assessors (realm 6 for RCT, NRCT and CBA).

Educational Interventions

Intervention affecting the prescriber's behavior

Among educational interventions, most aimed at changing the prescriber's behavior in relation to increased prescription of generic drugs[3,17,18,25,26,31-32] or reduced prescription by the reference name[16]. These interventions showed small to average increase in generic prescription and average reduction in the prescription by the reference name, but the quality of evidence of these studies was very low (Chart 3).

Among educational interventions focused on increasing generic prescriptions, Wensing et al.[18] held periodic meetings with small groups of 8 to 14 prescribers to report generic prescription rates and feedback on good prescribing practices. The intervention group showed a prescription increase of 0.75% (95% CI: 0.40-1.10) of the increase obtained in the control group. While the intervention group increased by 3.2%, the control group increased by 4.3%. (Chart 1)

Niquille et al.[25], Wensing et al.[30], Rausell Rausell et al.[17], Calvo Alcántara et al.[3], Walker & Mathers[26], López-Picazo Ferrer et al.[32], Sicras Mainar & Peláez de Loño[32] and Mastura & Teng[16] evaluated the effect of continuing education and feedback of prescriptions.

Wensing et al.[30] evaluated the feedback of prescribing information for 177 prescribers in educational sessions. This intervention had a small impact [OR 1.10 (95% CI: 1.08-1.13)]. Niquille et al.[25] evaluated the effect of continuing educa-

Chart 3. Evaluation of the quality of evidence and summary of the impact of interventions geared to the promotion of the use of generic drugs.

Educational Intervention				
Studies' population	Physicians and users in general, members of the same health plan			
Context	High- and upper-middle income countries; High HDI countries			
Intervention	Educational intervention focusing on prescriber, pharmacists or users			
Comparison	Lack of educational intervention			
Outcome	**Number of studies**	**General Evidence Quality Score[a]**	**Intervention Impact[b]**	**Comments**
Change in prescriber's behavior				
Prescription of generic drugs	8 (4 NRCT[1], 3 CBA[2], 1 ITS[3])	Very low	Small to average increase	The impact of educational interventions on the prescriber's behavior is uncertain, since the quality of the evidence was low, especially because of the high risk of bias in the studies considered, as well as the design, since most were observational.
Prescription of reference medicine	1 (CBA[4])	Very low	Average reduction	
Change in pharmacist's behavior				
Replacement of the reference medicine with generic drug	1 (RCT[5])	Moderate	Small increase	It is likely that the educational intervention has affected the pharmacist, but this effect has been minimal.
Change in user's behavior				
Replacement of the reference medicine with generic drug	1 (NRCT[6])	Low	Large increase	The replacement of the reference medicine with the generic drug has had a large increase effect, but the quality of evidence was low and outcome has been inaccurate.
(1) Wensing et al.2009, Niquille et al. 2010, Rausell Rausell et al. 2005; Calvo Alcântara et al.1999; (2) Wensing et al. 2004, Walker et al.2002, Sicras Mainar et al. 2005; (3) Lopez-Picazo Ferrer et al. 2002; (4) Mastura et al.2008; (5) Knowlton et al.1994; (6) Sedjo et al. 2009				
Financial Incentive				
Studies' population	Users on antihypertensive treatment			
Context	High income country; High HDI country (EU)			
Intervention	Change or introduction in the financial incentive			
Comparison	Free first treatment or payment at market value			
Outcome	**Number of studies**	**General Evidence Quality Score[a]**	**Intervention Impact[b]**	**Comments**
Change in prescriber's behavior				
Prescription of generic drugs	3 (1 RCT[7], 1 CBA[8], 1 ITS[9])	Moderate	Small increase	It is likely that the impact of financial interventions on the prescriber has an effect, but this effect is limited.
Change in user's behavior				
Relative use of generic drug compared to reference medicine	1 (1 ITS[10])	Very low	Average increase	The impact of financial interventions on users' behavior is uncertain, given the quality of the evidence.

it continues

tion and feedback of prescriptions for physicians between 1999 and 2007, however, information on generic drugs was shown only in the last four years (2004-2007), data shown were for five classes of drugs, with no general data on the effect of the intervention (Chart 1).

Rausell Rausell et al.[17] evaluated the effect of personalized monthly reports containing pre-

Chart 3. continuation

(7) Bhargava et al. 2010; (8) Scott et al. 2007; (9) Lopez-Picazo Ferrer et al. 2002; (10) Dunn et al. 2006				
Electronic Prescription				
Studies' population	Physicians			
Context	High income country; Very high HDI country			
Intervention	Introduction of electronic prescription			
Comparison	Lack of electronic prescription			
Outcome	**Number of studies**	**General Evidence Quality Score**	**Intervention Impact**	**Comments**
Prescription of generic drugs	2 (1 CBA[11], 1 ITS[12])	Very low	Small and large increase	The impact of electronic prescription interventions on prescriber behavior is uncertain, since the quality of the evidence was very low.
(11) Fischer et al. 2014; (12) Stenner et al. 2010				
Management (reform of the United Kingdom's National Health System)				
Studies' population	Physicians			
Context	High income country; Very high HDI country			
Intervention	Introduction of Fundholding (budget ceiling managed by physician)			
Comparison	Lack of Fundholding			
Outcome	**Number of studies**	**General Evidence Quality Score[a]**	**Intervention Impact[b]**	**Comments**
Prescription of generic drugs	1 CBA[13]	Very low	Small increase	The impact of regulatory interventions on prescriber's behavior is uncertain, since the quality of evidence was very low.
(13) Bradlow et al. 1993				

[a] Quality of evidence general score:
Moderate: The true impact value is likely to be close value found, but it could possibility be substantially different.
Low: The true impact value could be substantially different from value found.
Very low: We are uncertain as to the true impact value.
[b]The impacts of interventions were classified as very large, large, medium, small or very small.

scription indicators, one of which was the percentage of generics, showing a significant difference (p = 0.041) between intervention and control groups in the first analyzed period (4-6 months intervention), with a generic prescribing mean of 3.13% (95% CI: 1.79-4.47) in the intervention group and 1.81% (95% CI: 1.08-2.54) in the control group. The results were sustained after 10-12 months intervention and had an average impact, although the overall quality of evidence was very low (Chart 3).

Walker & Mathers[26] held meetings with prescribers, preceded by reports containing the comparative costs of prescription, number of items and share of generics. There was no significant difference between the groups studied in this study. Calvo Alcántara et al.[3] conducted educational sessions, prescribing reports and distributed the list of selected generic drugs, resulting in a significant change in prescriber behavior.

After implementing their feedback interventions on prescriptions and meetings, Sicras Mainar et al.[31] and Mastura et al.[16] found a significant change in the prescriber's behavior (Chart 1).

These studies[3,16-18,25,26,30-32] showed small to medium impact, always favorable to generic prescription, but with very low quality evidence (Chartes 2 and 3).

Interventions affecting the pharmacist's behavior

Knowton & Knapp[33] evaluated the impact of pharmaceutical meetings on pharmaceutical care, rational use of medicines and guidance in community pharmacies. Meetings were geared to teach pharmacists how to help their patients

Table 1. Evaluation of risk of bias of selected studies on interventions that promote the use of generic drugs.

Authors	Realms evaluated								
RCT[a]	**(1)[b]**	**(2)[b]**	**(3)[b]**	**(4)[b]**	**(5)[b]**	**(6)[b]**	**(7)[b]**	**(8)[b]**	**(9)[b]**
Bhargava et al. 2010	L	L	L	L	L	L	L	L	H
Knowlton & Knapp 1994	L	U	U	L	L	L	L	L	H
NRCT[a]									
Niquille et al.2010	H	H	U	U	U	L	L	H	H
Sedjo & Cox 2009	H	H	L	L	L	L	U	L	H
Wensing et al.2009	H	H	L	U	U	L	U	L	H
Calvo Alcantara et al. 1999	H	L	L	L	U	L	L	L	H
Rausell Rausell et al. 2005	H	H	L	L	U	L	L	L	H
CBA[a]									
Scott et al. 2007	H	H	L	U	U	L	L	L	H
Wensing et al.2004	H	H	L	L	U	L	U	L	H
Walker & Mathers 2002	H	H	L	L	U	L	U	L	H
Bradlow & Coulter 1993	H	H	L	U	U	L	L	L	H
Fischer et al. 2014	H	H	L	L	U	L	L	L	H
Mastura & Teng 2008	H	H	L	U	L	L	L	L	H
Sicras Mainar et al. 2005	H	H	L	U	L	L	L	L	H
ITS[a]	**(1)[c]**	**(2)[c]**	**(3)[c]**	**(4)[c]**	**(5)[c]**	**(6)[c]**	**(7)[c]**		
Stenner & Jonhson 2010	L	L	L	L	U	L	H		
Dunn et al. 2006	L	L	L	L	U	L	H		
Lopez-Picazo Ferrer et al. 2002	L	L	L	L	U	L	H		

H High risk of bias U Uncertain risk of bias L Low risk of bias

[a] RCT = Randomized clinical trials; NRCT = Non-Randomized Controlled Trials (NRCT); CBA = Controlled Before-After; ITS = Interrupted Time Series (ITS)

[b] Realms evaluated for RCT, NRCT and CBA: (1) generation of random sequence; (2) concealment of allocation; (3) measure of similar outcome in the intervention and control group; (4) baseline study results similar between control and intervention; (5) blinding participants and professionals regarding the allocation of intervention; (6) blinding outcome evaluators; (7) incomplete outcomes; (8) reporting of selective results; (9) other risks of bias.

[c] Realms evaluated for ITS: (1) independent observation in relation to other changes; (2) intervention effect form; (3) probability of intervention affecting data collection; (4) blinding participants and professionals regarding the allocation of intervention; (5) incomplete outcomes; (6) reporting of selective results; (7) other risks of bias.

talk to prescribers about choosing between brand name medicines and generic drugs. The impact of this intervention was small, with a 6.3% increase in the intervention group when compared to the control group. The overall quality of evidence on the pharmacist's behavioral change was moderate (Chartes 2 and 3).

Interventions affecting the user's behavior

Sedjo & Cox[35] evaluated the replacement of the reference medicine with the generic drug. This study evaluated educational dissemination, encouraging compliance with the use of drugs for chronic diseases and increasing acceptance of alternatives of generic drugs. While this educational intervention showed a substantial increased impact, the quality of this evidence was low, since the confidence interval of findings was broad (ORadj = 29.82 95% CI: 4.41-201.93) (Chartes 1, 2 and 3).

Financial incentive interventions

Interventions affecting the prescriber's behavior

López-Picazo Ferrer et al.[32] carried out educational and financial incentive intervention. This study indicated an absolute increase of 14.8 p.p. in generic prescriptions after intervention (from 2.79% to 17.63%), with a reported average impact (Chart 3).

Bhargava et al.[36] and Scott et al.[37] made financial interventions on the prescriber. The study subjects of Bhargava et al.[36] were primary care

prescribers who received detailed information and generic drug vouchers to deliver to users. In this study, the estimated effect of the voucher on the dispensing rate was an increase of 1.77 p.p. (p = 0.047), which is a very small impact (Chartes 1 and 2).

Scott et al.[37] evaluated the implementation of an automated system for the supply of samples of generic drugs in clinics, together with detailed information on generics. The intervention group showed a 7.5 p.p. increased rate of generic drugs dispensed, while the control group increased by 6.3 p.p. The difference in the first follow-up year was 1.2 p.p. and fell to 0.8 p.p. in the second year, which is a small impact, despite the overall moderate quality of evidence (Chart 2).

Interventions affecting the user's behavior

The financial incentive by Dunn et al.[4] had an average impact, but the quality of evidence was very low (Chart 2). This work evaluated the introduction of a generic incentive program.

Intervention through electronic prescription

Interventions affecting the prescriber's behavior

Fischer et al.[38] and Stenner et al.[39] evaluated electronic prescription as an intervention. In both studies, electronic prescription system highlighted the generic drug, and the prescriber was able to choose. Fischer et al.[33] evaluated the proportion of drugs in each of the three drug co-payment groups of the American health system. The increased proportion of generics prescribed after the intervention was of 4 p.p., which is a very small impact. In the study by Stenner et al.[39], the proportion of generics increased from 32.1% to 54.2% (22 p.p. increase) in the group that used the electronic system and from 29.3% to 31.4% in the control group (Chart 1), with very low quality of evidence (Chart 3).

Managerial intervention

Interventions affecting the prescriber's behavior

This intervention stemmed from UK's NHS reform[40], which made it possible for doctors to be responsible for part of the budget, receiving and managing a budget ceiling (Fundholding). The proportion of generic drugs prescribed by clinic doctors who receive this budget ceiling was compared to that of clinics that did not receive it. After the intervention, the intervention group increased 7.6% (95% CI: 7.2-8.0), whereas the control group increased only 0.1% (95% CI: 0.2-0.4) (Chart 1). This intervention had a small impact and the quality of evidence was moderate (Chartes 2 and 3).

Discussion

Educational interventions were the most frequent in this review, as was done by Babar et al.[1]. These are widely used to promote behavioral change, but impact was small in the studies analyzed, which may have occurred due to the low quality of evidence. While these interventions showed a significant individual behavior change, the proportions of increase of generic were not significant, not exceeding 22 p.p. increase. The difference in the magnitude of studies may be due to their different settings, user type and medical specialties involved[3,17,18,26,31].

All studies were performed in high or high middle-income countries and used secondary data. These countries have health records, including prescriptions records, which are reliable and can be quickly used to evaluate and/or monitor interventions. In addition, most work with electronic prescriptions and interconnected dispensing and co-payment systems that facilitate access to intervention outcomes and monitoring of prescriptions[43].

The selected studies were conducted between 1993 and 2010, and showed a lack of current studies addressing increased use of generics, indicating a greater concern with the expanded use of generics when they were implemented. However, some countries still evidence a low proportion of generic drugs in the market when compared to others[6], suggesting the need for interventions to increase their use.

The quality of evidence shown by studies was very low or low, evidencing the need for better designed and executed studies to improve the quality of evidence[3]. Babar et al.[1] performed a narrative review without a quality evaluation. On the other hand, Moe-Byrne et al.[20] evaluated the quality of some of these studies, but it was merely a narrative evaluation and did not perform an impact assessment through data summarization, as shown in this review.

Most studies were performed in a hospital environment or primary care clinics, and generic prescription was one of the indicators of the

quality of prescription evaluated[18,30]. Although there has been no significant increase in generic prescription, this is an important indicator in the hospital setting, since it is also used as an expense indicator and replacement with generic drugs leads to reduced expenses[44-46]. Measures that curb health costs caused by medicines are necessary, and replacement with generic drugs is one of them.[1]

Studies such as those of Bhargava et al.[36] and Sedjo & Cox[35] carried out in the U.S., the country that launched generic drugs and showed high rates of use reinforce the quality and reliability of these medicines, contributing to the continued increase of their use.

Another important consideration is the polysemic definition of medicines, since different countries use different definitions[11] and most of the studies analyzed here do not bring the definition of a generic drug and may lead to a misinterpretation about replacement, use and prescription of generic drugs.

However, by analyzing drug policies and the definitions of generics used in each of the six countries of origin of the studies of this review, it was observed that they use similar definitions, and generic drugs are those that show the same active principle, the same pharmaceutical form, dose, concentration, route of administration as the reference drug, seeking to ensure the quality and safety of these drugs[47-49].

In the study by Dunne et al.[50], knowledge about generics, both for pharmacists and prescribers was surveyed several times in the interviews. Thus, the belief that adequate knowledge by health professionals and the population in general is an essential aspect of acceptance and improvement of their use[50].

Regarding the financial incentive applied to users, Schafheutle et al.[51] suggest that most users are, to a greater or lesser degree, cost-conscious when it comes to managing their condition and their medications. This would occur especially with those who need to pay for dispensing their prescriptions. Thus, the cost realm becomes an important factor[51]. Interventions that implement financial incentives can promote replacement by increasing the use of generic drugs. However, it should be noted that the pharmaceutical industry and health plans in some countries might have a strong influence on policies favoring the use of generic drugs[52-55].

Two studies evaluated electronic prescription as an intervention to increase the use of generics[38,39], the fact that the name of the generic drug is available as the first choice, only requiring selection to compose the prescription, may not only increase the prescription of generics, but also improve its quality. Electronic prescription is available in many hospitals, but without highlighting generic drugs. This seemingly simple and low-cost intervention could be implemented in these health services in order to improve prescription.

Only one study with managerial intervention was included in the review[40]. This type of intervention, despite being applied to prescribers and dispensers, is more comprehensive and can reach more professionals, changing the prescription behavior. This intervention allowed the prescriber to manage part of the costs of the health facility, including medicines. Part of the savings was refunded to the prescriber himself. Thus, this strategy leads to the prescription of generic drugs because of their lower cost[40].

One of the criteria for choosing the analyzed databases was the facilitated access by authors. This may have left out some relevant bases, such as SCOPUS. However, the databases consulted have a broad scope in the subject studied.

Finally, no recalculation of the results for standardization of outcome measures was performed, since the heterogeneous presentation of results facilitated the quantification of findings.

Conclusions

This review lacks studies with a robust methodology to judge the impact of the interventions that have been implemented in order to increase the use, prescription or dispensing of generics. In addition, the few existing studies had small impact and low quality of evidence. Most of the studies analyzed addressed interventions that involved, directly or indirectly, the issue of the lowest price of generics, highlighting concern about drug expenditure. We emphasize the lack of recent studies conducted in middle- and low-income countries. This topic is of interest, since three recent reviews have been identified, although with different approaches, and have shown interest in analyzing what has been done to increase the use of generics. Thus, we highlight the need for well-designed interventions, especially in low- and middle-income countries to obtain clearer evidence.

Collaborations

MC Guttier performed the search and selection of the articles and drafted the manuscript. MPT Silveira performed the selection of the articles and reviewed the manuscript. VL Luiza contributed to the selection and helped to draft the manuscript. AD Bertoldi helped to draft the manuscript. All authors read and approved the final manuscript.

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Article submitted 26/10/2016
Approved 10/04/2017
Final version submitted 12/04/2017