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Review Article

Medicine Interchangeabilty in Brazil, is it Safe? A Systematic Review for the Last 15 Years about Oral Drugs

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ABSTRACT

Objectives: The goal of this study was to review studies about bioequivalence test (BE) for oral drugs interchangeability in Brazil.

Methods: We searched two databases with a strict inclusion process: Conducted in Brazil; humans volunteers; cover the period from 2004 to 2019; be a comparative study between oral formulations; at least one Brazilian formulation under test and published in periodic; Two reviewers independently extracted the data.

Results: 4628 articles screened; 68 articles were included. 67 applying clinical assays and 1 article Chow and Liu methodology. Across studies that evaluated BE by clinical assays 66 demonstrated BE comparing generic or similar to their reference medicine.

Conclusion: These data can be used to inform interventions to change the public's beliefs about a safe use of generic or similar drugs; and avoiding substitution between copies.

Keywords: Bioequivalence; Interchangeability; Oral Drugs

INTRODUCTION

In Brazil, 3 medicines types are known: i) reference medicine, responsible for introduction of a new drug on market and has patent protection, ii) generic medicines and iii) similar medicine both developed after innovative medicine patent protection expires [1,2]. According to ANVISA (Brazilian Health Surveillance Agency) guidance, similar medicines may differ in characteristics relative to size, shape, shelf-life, packaging, labeling and excipients to their reference [2]. Generic medicines it may differ only in excipients and a simplified version of the chemical name is displayed on the packaging including also a yellow stripe with the letter "G" to indicate it [2].

Concerning oral administration medicines, a resolution n°. 391 of 1999 introduces generics into Brazilian Pharmaceutical market and since the beginning it was essential to prove pharmaceutical equivalence (PE) as well as bioequivalence (BE) to their reference [1]. About similar medicines, proceeding a resolution n°. 134 of 2003, they all must to follow PE and BE requirements. Before that legislation, similar medicine met PE tests only [2].

For instance, it is assumed that two medicines (X and Y) are under these tests. PE is achieved when just *in vitro* tests are made to evaluate whether both contain the same concentration drug as also attending all quality requirements [3]. Otherwise BE is a comparative study of bioavailability profile of these medicines *in vivo*. X and Y fulfil BE whether bioavailability parameters as Peak concentration ($_{Cmax}$), time to peak concentration and extent of absorption (area under the curve) not present a significant statistical difference after administration on the same dose under same conditions in patients [4]. Therefore, PE not assures a safety substitution between medicines [5].

In addition, bioequivalence tests are performed to evaluate plasma concentration of the active moiety or metabolite in function of time. From these data, concentration time curves are used to assess the pharmacokinetic parameters mentioned [6]. According to Brazilian legislation BE between two formulations is established obeying 90% confidence interval, within range of 80% and 125% for C_{max} and AUC [7]. Although that, due of an initial laws gap about similar medicines, attached by several quality deviations leading to some generic recall, a lack of confidence among population and prescribers remains. In addition, BE between medicine copies (Generic and Similar) are not guarantee of treatment success. But it is common for patients to replace one by other [8].

Is it safe change a reference oral drug by its copies? If copies are interchangeable to its reference why is it not advisable a substitution

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between them? The review purpose is to bring studies to clarify Brazilian interchangeability scenario.

LITERATURE SEARCH

Search and information sources

This review was conducted up to December 23, 2019, using search terms as "bioequivalence and Brazil", "Oral drugs bioequivalence and Brazil" in attempt to cover all inclusion criteria and article objectives. Electronic databases Pubmed and Academic Scholar were used.

Study selection

Two reviewers (L.G.S and S.G.R) screened title and abstracts followed by full texts lectures of relevant articles. A third reviewer (S.D.M) analyzed and resolved any disagreements.

Inclusion and exclusion criteria

Articles must to attend these following inclusion criteria: conducted in Brazil, in human volunteers, cover the period from 2004 to 2019, be a comparative study between oral formulations; at least one Brazilian formulation under test and published in periodic. In addition, biowaiver monographs, comparison between different dosage forms and articles with incomplete or inaccessible data were excluded.

Synthesis of results

Figure 1 summarizes the methods used for data synthesis. Data extraction division was executed in order to separate methodologies applied. For instance, the idea of Chow and Liu methodology is to assure statistically BE between copies based on independent data from BE studies executed when compared to their reference [9].

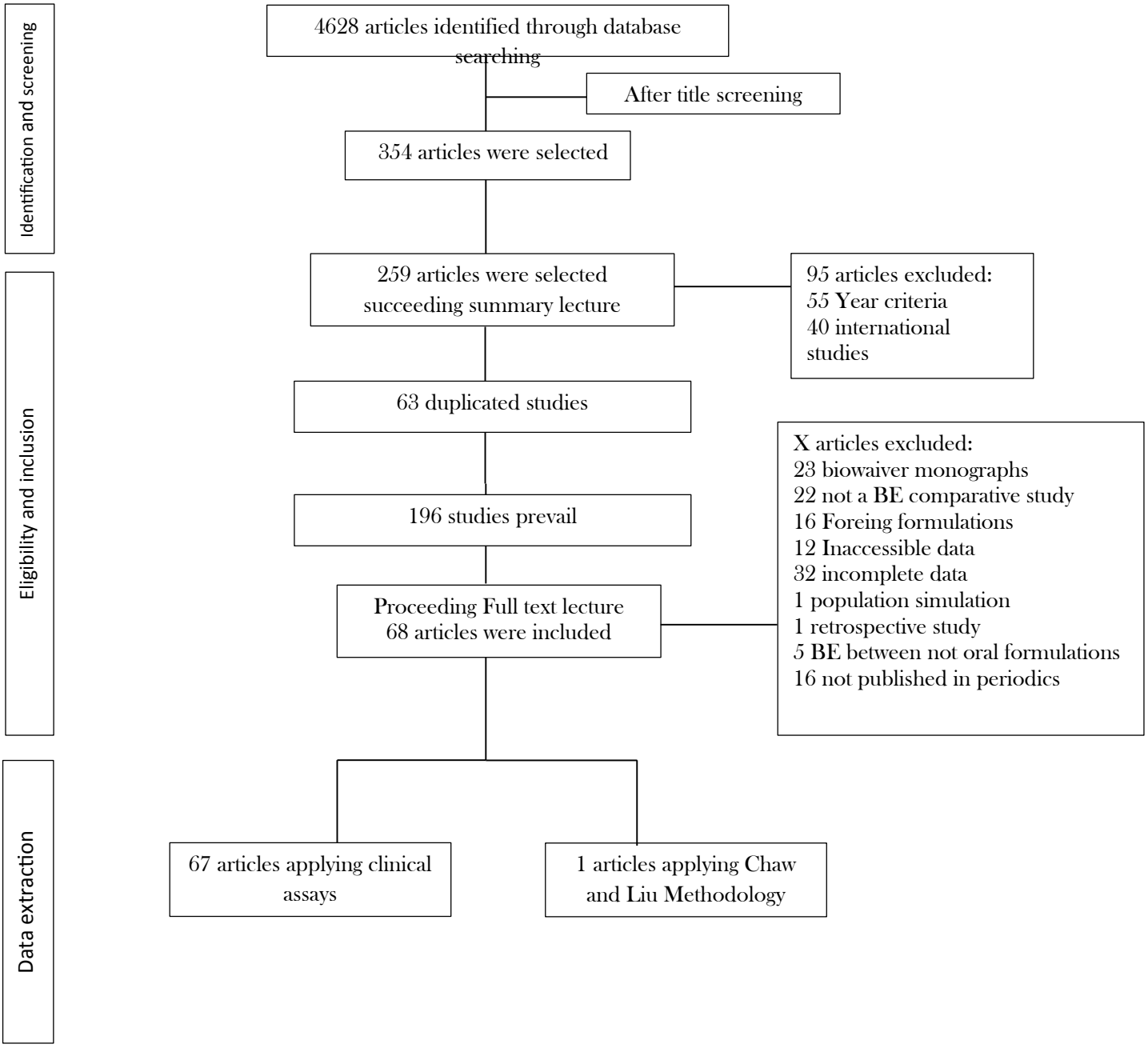


Figure 1: Summary of systematic review process.

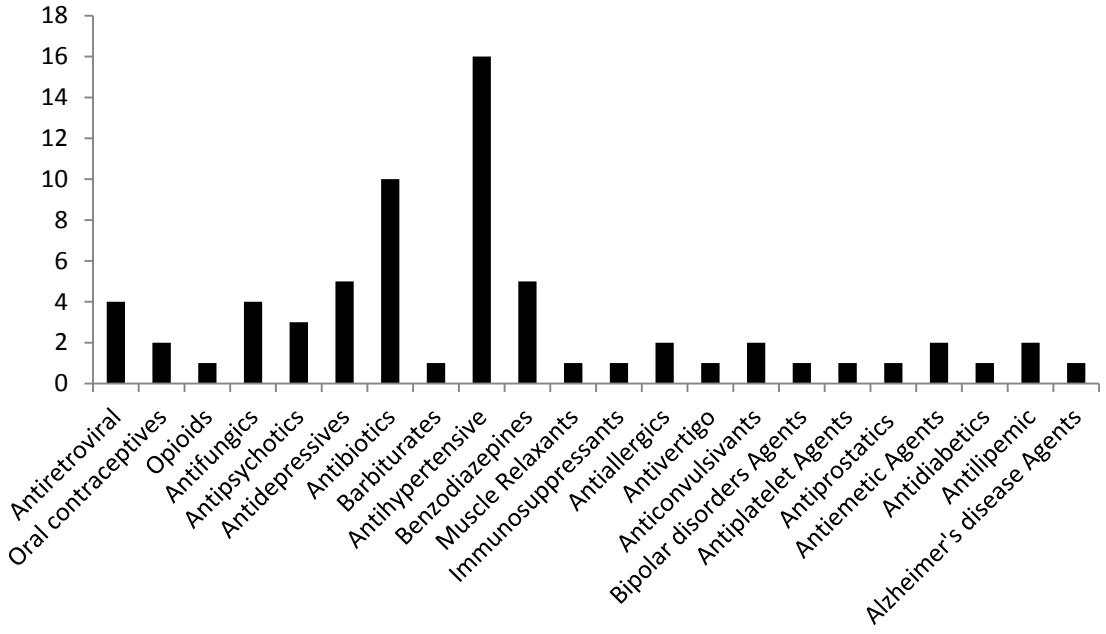
RESULTS

It was identified 67 studies which involved a total of 2185 subjects. Graph 1 shows BE studies divided by classes and indications. Graph 2 shows BE studies divided by types of medicines submitted to comparison. Across studies that evaluated BE by clinical assays 66 demonstrated BE comparing copies to their reference [10-75].

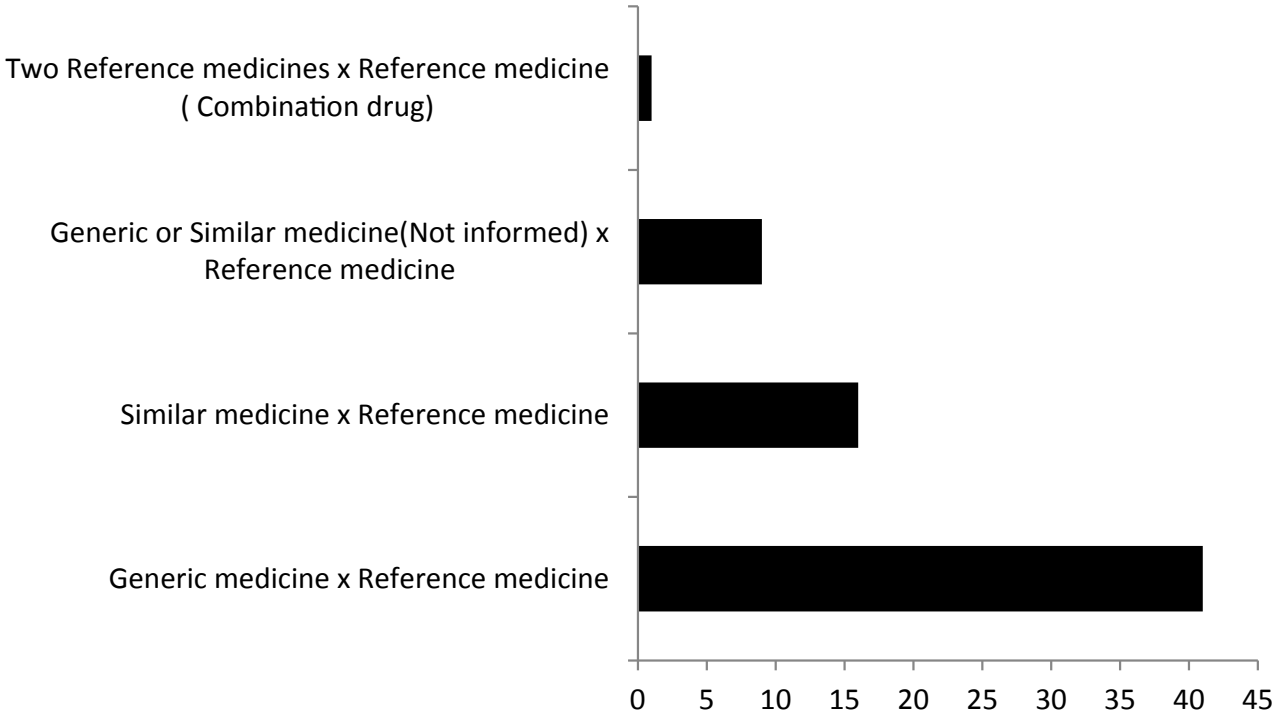
Only 1 study indicated not BE analyzing generic or similar with their reference medicine. A total of 22 subjects received a single 2-mg dose of similar and reference risperidone. Pharmacokinetic and statistical analyses were executed; both Cmáx and AUC parameters left the range established by legislation [76].

The study which applied Chow and Liu methodology has reported BE data comparing generic, similar and references drugs each other. During its meta-analysis between three formulations containing hydrochlorothiazide it was observed that all copies was BE when compared to their reference. In a comparison between copies, 1 of 3 combinations has concluded to non-bioequivalence. In this case, Cmax parameter left the range established by ANVISA, avoiding BE and consequently interchangeability for these combinations [77].

In addition, 8 formulations containing enalapril was compared to its reference drug, all of them fitted established limits. But it was observed that 14 of 28 combinations concluded by non-bioequivalence for Cmax parameter. Regarding AUC 6 of 28 combinations concluded non-bioequivalence [77].



Graph 1: Numbers of studies by drug classes.



Graph 2: Numbers of studies separated by type comparison.

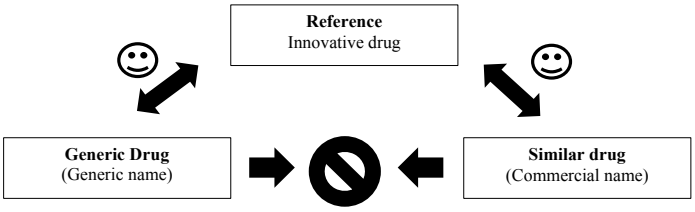


Figure 2: Schematic illustration about current legislation. Interchangeability between copies is forbidden. Interchangeability is allowed between copy and reference.

DISCUSSION

It is suggested that interchangeability is safe between copies with their reference. In addition, bioequivalence tests are performed to launch a copy on the market comparing pharmacokinetic parameters with their originator medicine [3,7]. Figure 2 summarizes the current legislation.

A typical case involves some professionals prescribe only reference medicines [78], but given this studies scenario the prescription of generic and similar might be more indicated.

Besides, prejudgment with medicines copies still remains among population, because of low price. They believe that price is synonymous with low quality raw material and added to the massive campaign by pharmaceutical industry to tarnish the image of generic, patients end up choosing the most expensive medicine [79].

Regarding the interchangeability between copies, even the legislation not allow [6], it was evidenced that it is not safe [77]. Bioequivalence studies allow a range of 80-125% in pharmacokinetic parameters, when comparing test drug with their reference as mentioned. Therefore, if one formulation has a deviation to upper side of the range when compared to another with deviation to opposite direction, when compared to each other they may possibly go beyond limits settled by legislation, not ensuring interchangeability between copies (generic and similar combinations).

This may result in a modified therapeutic response because these formulations are, mostly, non-bioequivalent when compared to each other [77-79]. It is clear that when therapeutic response is lower than expected, drug does not achieve appropriate amounts to produce an expected effect in the body [80]. Same direction, an excess in absorption may lead to drug toxic levels in the organism [81].

For example, in studies involving contraceptive formulations copies were bioequivalent only in comparison to their reference. But security between copies cannot be guaranteed. Therefore, recurrent practices in women switching generic formulations should be avoided. In addition, the alert is also valid for medicines used to control the chronic diseases most common here in Brazil, as well as for drugs with narrow therapeutic window.

CONCLUSION

Across analysis it was evidenced a majority of results indicating a safe substitution between similar or generic to their reference. Generic and similar drugs frequently are not bioequivalent when compared each other. Orientation guidance for health professionals is needed. Pharmacists dealing directly with patient has to be aware about the insecurity of interchangeability between generic and similar, especially those with narrow therapeutic window and regular use. These data can be used to inform interventions to change the public's beliefs about a safe use of generic or similar drugs; and avoiding substitution between copies.

CONFLICTS OF INTEREST STATEMENT

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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