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Review article

Therapeutic equivalence of antipsychotics and antidepressants – A systematic review

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ABSTRACT

The number of newly approved generic psychotropic drugs increases every year and, in many countries, their sales exceed the sales of brand-name counterparts. In order for any generic drug to receive an approval of regulatory authorities, its bioequivalence with the corresponding reference product must be demonstrated. Moreover, generic drugs must meet the same quality standards as reference drugs. However, many psychiatrists express concerns about use of generic drugs. We carried out a systematic analysis of the relevant literature indexed in PubMed and Cochrane databases. The MeSH term "generic" was combined with terms describing antipsychotic and antidepressive drugs, including their pharmaceutical names and relevant mental disorders. All 26 articles including either clinical studies or case reports have been qualified for a detailed analysis. No cases describing switches between two generics were found. Therapeutic equivalence studies evaluating antipsychotics included clozapine, olanzapine, and risperidone. The clinical status was judged to have worsened in 15.7% patients treated with clozapine. The number of relapses before and after the switch was not significantly different in patients treated with olanzapine. Two case reports showed clinical state deterioration after switch to generic risperidone. The clinical outcome after conversion to a generic antidepressant was evaluated only in one retrospective study. That study analyzed the outcomes of treatment with citalopram and revealed mental state deterioration in 11.6% of patients. Only single reports describe cases of impaired efficacy or adverse events after the switch to a generic antidepressant, including fluoxetine, mirtazapine, and venlafaxine. No cases of suicidal attempt after the switch were reported.

Although the overall number of described cases is rather modest, health professionals should be aware of possible changes in the therapeutic effectiveness after changing to a generic medicine.

Contents

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Introduction

Hatch-Waxman Act and bioequivalence guidelines released by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) that define the rules of registration of generic drugs have been among the most important regulatory documents, allowing a wide access to modern drugs in psychiatric pharmacotherapy [1,2]. The number of newly approved generic psychotropic drugs increases every year and, in many countries, their sales exceed the sales of brand-name counterparts. Generic drugs can be granted their marketing authorization for identical indications to those of reference drugs. Prescription and over-the-counter generic drugs that are marketed in the European Union and the United States must all meet standards established by EMA and FDA, respectively. According to Directive 2001/83/EC of the European Parliament, a generic medicinal product is "a medicinal product which has the same qualitative and quantitative composition of active substances as the reference medicinal product, the same pharmaceutical form as the reference medicinal product, and which bioequivalence with the reference medicinal product has been demonstrated by means of appropriate bioavailability studies."

Both EMA and FDA require the Abbreviated New Drug Application (ANDA) for a generic drug to only demonstrate its bioequivalence with the reference product. Submission of the outcomes of preclinical or clinical studies that establish the efficacy and safety of the active ingredient is not required for a generic drug as these data would have previously been documented during the approval of the innovator product. Moreover, the aim of the required bioequivalence studies is to compare generic and reference drug's absorption. The absorption can be assessed by measuring the maximum plasma concentration (C_{max}) and the area under the curve (AUC) of "drug plasma concentration against time". C_{max} is an indirect measure of the rate of absorption and it may relate to drug's toxicity and/or efficacy. AUC reflects the entire exposure to the drug. Both FDA and EMA accept C_{max} and AUC to vary from −20% to +25% between reference and generic products [3]. The use of these criteria is based on medicinal experts' consensus that such range of differences in the active ingredient concentration in the plasma will not significantly affect either the efficacy or safety of the drug. A retrospective analysis of 2070 bioequivalence studies of generic drugs approved by the FDA in a 12-year period showed that an average difference in C_{max} and AUC between generic and reference products was 4.35 and 3.56%, respectively [4]. Bioequivalence studies are generally conducted in healthy adult volunteers of both sexes under standardized conditions. However, in case of clozapine the FDA released in 2005 a guideline recommending its bioequivalence studies to be conducted in patients with schizophrenia at therapeutic doses [5]. Administration of clozapine doses higher than 12.5 mg to healthy volunteers is considered unethical due to a risk of serious adverse events, such as hypotension, bradycardia, or even syncope and asystole. Of note, the doses tolerated by schizophrenic patients can be even 60 times higher [6].

Most bioequivalence studies use the "single dose, two-way crossover" design, and it is recommended to conduct bioequivalence studies on the highest strength of the drug. Whereas differences in shape, color, excipients, the particle size, and the crystalline form of the active ingredient are acceptable, it is required to demonstrate that the dissolution profiles of the generic and the reference medicinal product are similar. Both the generic and the reference drug must meet the same standards for manufacturing and quality, according to relevant regulations [7].

Even though the requirements for bioequivalence are well established, many psychiatrists and their patients express concerns about generic drugs [8].

As head-to-head studies comparing efficacy and safety of reference and generic medicines are considered ethically unacceptable, retrospective observational studies and case reports are the only source of data on the therapeutic equivalence of generic drugs.

We have performed a systematic review to synthesize data from all available studies and case reports on both clinical and pharmacological aspects of bioequivalence as it applies to antipsychotic and antidepressive drugs.

Methods

Data sources

We have searched two electronic databases, MEDLINE (*via* PubMed) and The Cochrane Library, as well as abstract proceedings of major scientific meetings, and bibliographies of all eligible studies and case reports, from the date of inception to the present (i.e., March 26, 2015). In addition, reference lists of identified reviews and selected trials were scanned for any other relevant trials. The search strategy included the medical subject headings of: Mental Disorders, Bipolar Disorder, Affective Disorders, Psychotic, Depression, Anxiety, Anxiety Disorder, and Schizophrenia. These terms were combined with terms representing the interventions, expressed as names of different