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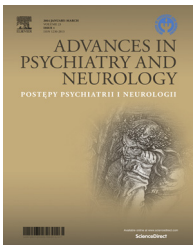

Review/Praca poglądowa

Bioequivalence and therapeutic equivalence of psychotropic drugs

Równoważność biologiczna i terapeutyczna leków psychotropowych

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ABSTRACT

Objective: It is the objective of this paper to discuss the requirements that must be met by generic drugs and explain basic concepts relating to bioequivalence. The authors have also included two tables listing the trading names of antidepressants and antipsychotics, with a valid authorization for marketing in Poland, which might prove helpful in daily psychiatric practice. **Views:** The introduction of regulations which enabled the registration of drugs equivalent to reference medicinal products (so-called generic drugs) has been one of the main breakthroughs in the psychiatric pharmacotherapy. Breaking with the monopoly resulted in lower prices and increased the accessibility of modern treatment methods. On the other hand, the effective period of market exclusivity is also the post-marketing period of monitoring for the safety and efficacy of these medicinal products. **Conclusions:** Drugs equivalent to reference (branded) products are the latest, up-to-date form of treatment, though their safety profile and efficacy are already well-known, owing to the long presence of the active substance on the market. Most of the publications confirm the therapeutic equivalence between the branded and generic antipsychotics and antidepressants. However, one should also keep in mind a potential change in the patient's clinical condition after replacing a reference product with its generic equivalent.

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Reference and generic drugs – similarities and differences

The definition of a generic product is provided by the Polish Pharmaceutical Law being a direct transposition of the regulations provided by the Directive of the European Parliament and the Council 2001/83/EC. According to the directive, a generic drug is ''a medicinal product with the same qualitative and quantitative content of active substances, the same pharmaceutical form as the reference product and also whose bioequivalence to the reference medicinal product has been confirmed by appropriate bioavailability studies'' [1]. This means that both the reference product and its equivalent contain the same active substances in equal doses. Reference products are admitted to the market only after their full documentation, including qualitative, preclinical and clinical studies has been compiled as they are only registered for the first time for a given active substance. Since generic products contain the same active substance in the same form there is no need to re-examine them as the properties of the substance have been investigated at the time of original registration of the reference drug. In order to register a generic drug, it is, however, a necessary requirement to conduct bioequivalence studies, aimed at proving that the generic drug is of a similar bioavailability. Bioavailability is a pharmacokinetic concept which determines the percentage of the drug's dose which passes into the systemic circulation after the extravascular administration, as well as the speed of the process. Differences in bioavailability can be caused, among other reasons, by incomplete release from the dosage forms, incomplete absorption, the first pass effect or a different composition of excipients. They may be also associated with different physicochemical properties of the product (friability, disintegration time, pharmaceutical availability of the active substance). Studies of pharmaceutical availability (also referred to as the release rate studies) are used to determine properties of the drug and are considered a key element in the assessment of pharmaceutical equivalence. Pharmaceutically equivalent products must meet the same requirements in terms of quality, purity and identity of the active ingredient. Studies on pharmaceutical availability also allow for the assessment of bioavailability, which is determined by the release of an active substance [2]. In order to obtain an authorization for marketing purposes, it is necessary to demonstrate the similarity of a generic drug to the reference formulation in both *in vitro* release and bioequivalence studies.

Bioequivalence studies

Based on years of research and reports available, it is assumed that medicines containing the same active substance in equal doses and without significantly different absorption levels have similar effects on the body. The ranges of similarity in the absorption of a reference drug and its counterpart, the methodology of bioequivalence studies required to ensure therapeutic equivalence, understood as identical clinical effect, have been developed and published by EMA [3]. Today all bioequivalence studies undertaken in the European Union countries are conducted based on these guidelines. Such studies assess bioavailability of a drug by measuring the pharmacokinetic parameters characterizing the degree (quantity) and speed of absorption of an active substance. Absorption is the first stage of the transformation that the drug undergoes in the body. It is at the same time the stage whose possible changeability depends on the drug itself. Among the factors affecting gastrointestinal absorption are: properties of the form of the drug and a degree of its ionization; other factors are personal variables (including the pH of the gastrointestinal tract, activity of digestive enzymes, and presence of chyme in the stomach, blood supply to the gastrointestinal tract or disorders of the gastrointestinal tract). Next stages of the drug's journey through the body are mostly dependent on the patient's individual characteristics, which is why investigating parameters other than absorption makes no sense in the context of trying to find out about the impact of two products containing the same active substance. Any possible differences at the following stages would only stem from the differences between individuals rather than between generic and branded medicines. It is worth emphasizing that the accepted range of tolerance of the parameters' similarity includes the differences resulting from temporal changes in the parameters between individuals [4].

According to the legal provisions defined by EMA, bioequivalence tests are conducted with the participation of minimum 12 healthy volunteers (in case of anticipated increased variability of pharmacokinetic parameters, there should be more volunteers). The inclusion criteria for these studies are very precise, for example with regards to the subject's age, which needs to be above 18, and BMI within the range of 18.5–30. Most bioequivalence studies use a single dose two-way crossover design. Each volunteer receives a reference drug and a generic drug, keeping the washout period, which ensures the elimination from the body of five half-lives of the drug. Based on the measurement of drug concentrations in biological fluids (usually serum), the following pharmacokinetic measures are determined: the area under the curve (AUC), maximum blood concentration (C_{max}) and time at which C_{max} occurs (T_{max}). Two drugs are then considered bioequivalent if the ratio of logarithmised values of the AUC and Cmax parameters for both drugs are in the range of 80–125% at 90% confidence interval. In the case of drugs with narrow therapeutic index, the range is 90–111% [5]. It should also be noted that the results of some of the bioequivalence studies are published in peer-reviewed journals with high impact factor (*e.g.* Clinical Therapeutics, Drugs) [6, 7].

Reasons for changes in patient's therapeutic response after the change into a new medicinal product containing the same active ingredient as the previously taken drug

Literature contains only a few isolated case reports that describe changes in therapeutic response and these are usually recorded in outpatient treatment. It is often the case