Pharmacological Reports 68 (2016) 217–223

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Therapeutic equivalence of antipsychotics and antidepressants – A systematic review

Grzegorz Cessak [a,b], Konrad Rokita [a,c], Marta Dąbrowska [a], Katarzyna Sejbuk– Rozbicka [a], Anna Zaremba [a], Dagmara Mirowska-Guzel [a,d], Ewa Bałkowiec-Iskra [a,b,c,*]

[a] Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warszawa, Poland
[b] The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Warszawa, Poland
[c] Nowowiejski City Hospital, Warszawa, Poland
[d] Second Department of Neurology, Institute of Psychiatry and Neurology, Warszawa, Poland

ARTICLE INFO

Article history:
Received 17 May 2015
Received in revised form 27 August 2015
Accepted 31 August 2015
Available online 11 September 2015

Keywords:
Antipsychotics
Antidepressants
Bioequivalence
Generic drugs

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

* Corresponding author.
E-mail address: ebalkowiec@wum.edu.pl (E. Bałkowiec-Iskra).

http://dx.doi.org/10.1016/j.pharep.2015.08.017

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

active substances: Amisulpride, Clozapine, Levomepromazine, Olanzapine, Quetiapine, Risperidone, Ziprasidone, Citalopram, Escitalopram, Mirtazapine, Fluoxetine, Fluvoxamine, Mianserin, Moclobemide, Paroxetine, Sertraline, Tianeptine, and Venlafaxine. These words were subsequently combined with the keywords developed for generic drugs. The search terms were developed based on MeSH headings. The search results, i.e., all titles, abstracts and keywords, were downloaded to a reference management database (Reference Manager, Thomson Reuters), and two researchers independently examined the selected references, based on the selection criteria described below.

Selection of studies

The project team created an eligibility assessment checklist based on the PICOS framework, in order to identify articles describing the efficacy and safety of generic drugs in comparison with proprietary drugs that would subsequently be included in this review. The articles were restricted to the following: (1) P (patient population)—conducted with patients with mental disorders, and not on healthy volunteers, (2) I (intervention)—involving antipsychotic and antidepressive drugs from our list, (3) C (comparison)—involving a brand-name drug with the same active substance as the studied generic drug, (4) O (outcome)—with study endpoints describing efficacy, safety, and pharmacokinetics of both drugs, i.e., generic and brand name, and (5) S (setting)—included all randomized controlled studies, nonrandomized studies (cohort and case-control studies), and case series, where the methodology was not restricted to specific types. In addition, all included articles have been written in English and published before March 26, 2015. Although the study itself could have taken place in any location of the globe, the brand-name drug used (or an identical formulation of it) must have been approved by the FDA or EMA. Articles were excluded if: (1) they did not report on the efficacy and safety of generic drugs; or (2) the efficacy and safety information was not apparent after reviewing the full article; or (3) the full text of the article was unavailable despite our best efforts to locate it.

Data extraction and synthesis

Two researchers independently screened the titles and abstracts of all citations using the eligibility assessment checklist. Abstracts were classified as relevant, potentially relevant, or not relevant. Relevant and potentially relevant abstracts were selected for a full review of the article. Abstracts of potentially relevant articles were further examined independently by two researchers. If there were discordance between two researchers on the relevancy of an abstract, a third reviewer read the abstract to determine its relevancy.

For studies included in the analysis, one researcher extracted data on study design, sample sizes, patient characteristics (i.e., the type and severity of disease, inclusion criteria), interventions (i.e., names of generic drugs, dosage), outcomes (i.e., change in scores of psychiatric scales), along with other information about methodology, sponsors, and performance sites. The described extraction of information was checked by a second researcher and, in case of any inconsistencies, a third researcher of the reviewing team verified the extraction once again.

Results

General information

Our literature search originally identified 132 articles. However, based on our inclusion criteria, 44 articles were qualified for full-text review, with additional 18 articles excluded after their full review. As a result, our screen identified 26 articles that qualified for a detailed analysis and have been included in this review.

Antipsychotic drugs

Clozapine

Overall, the studies were heterogenous both in design and parameters under evaluation. In total, 636 patients were included in the clozapine studies alone (Table 1). The clinical status, assessed by such means as clinical scales, a general psychiatric examination, a need of dose adjustment or medical service utilization, was judged to have worsened in 100 patients (15.7% of all patients included in the studies) and improved or not changed in 536 patients (84.3%).

Clinical outcomes

Therapeutic equivalence of the generic and its reference drug was evaluated directly, either by psychiatric scales or by a general

Table 1
Clinical measures of a switch from reference to generic clozapine.

Source	Type of study	Clinical measure	Number of patients who deteriorated after the switch [a]	Number of patients who improved or stayed the same after the switch [a]
Lam et al. (2001)	Randomized, blinded crossover	PANSS	1	20
Kluznik et al. (2001)	Randomized, blinded crossover	"Psychotic relapse"	14	31
Mofsen and Balter (2001)	Uncontrolled, observational	General psychiatric state examination	13	12
Sajbel et al. (2001)	Uncontrolled, observational	General psychiatric state examination	–	16[a]
Stoner et al. (2003)	Uncontrolled, observational	CGI-I[b]	6	18
Paton et al. (2006)	Uncontrolled, observational	CGI-I	19	285
Makela et al. (2003)	Uncontrolled, observational	PANSS	–	18[c]
Healy et al. (2005)	Retrospective	Dose adjustment	39[d]	69
Alessi-Severini et al. (2006) [e]	Retrospective	Dose adjustment	8	50
Oluboka et al. (2010)	Randomized, blinded crossover	GAS	–	17

PANSS, positive and negative syndrome scale; CGI-I, clinical global impression-improvement scale; GAS, global assessment scale.

[a] One patient experienced difficulties with compliance. Since no information was given whether the patient improved or deteriorated, this individual was not included in our analysis.

[b] Clinical state was assessed by either CGI scale or BPRS. Since Paton et al. (2006) used CGI, we have included here the results of CGI for a better comparability. For BPRS, the outcomes were as follows: 2 patients deteriorated, whereas 22 improved.

[c] Two patients were excluded from the study because, in the meantime, they were admitted to the hospital and could no longer be evaluated under the generic product.

[d] Patients who required a change in the dose, or an addition of another antipsychotic, or had a change in adjacent antipsychotic, were all included.

[e] Clinical state was also assessed by medical service utilization, and it did not differ between groups.

psychiatric examination. Among 45 patients included in the study by Kluznik et al., 16 patients experienced clinically significant worsening (14 patients during the treatment with generic clozapine) which manifested itself as increases in irritability, insomnia, anger, anxiety, and a marked exacerbation of positive psychotic symptoms [9]. In the study by Stoner et al. only two of 24 patients experienced clinical state deterioration after conversion to generic clozapine [10].

In study by Paton et al. out of 337 patients converted to generic clozapine, the mental state improved in 92 patients, deteriorated in 19 patients, and stayed the same in 193 patients [11].

In the open-label study by Makela et al. no statistically significant differences in Positive and Negative Syndrome Scale (PANSS), Beck Anxiety Inventory (BAI), Abnormal Involuntary Movement Scale (AIMS), or Movement Disorder Assessment (MDA) scale were noted after conversion of 18 patients from reference to generic clozapine [12].

In a group of 17 patients switched to generic clozapine, there was a significant increase in global assessment scale (GAS) scores by the end of a 6-month observation period, compared with baseline scores obtained during the reference treatment, suggesting a better clinical outcome of treatment with the generic drug [13].

In the study by Mofsen and Balter, seven out of 25 patients experienced a significant reemergence of previously well-controlled psychotic symptoms (e.g., inappropriate sexual behaviors, religious preoccupation, obsessive-compulsive behaviors, social isolation, spontaneous crying, violent and verbally abusive outbursts, auditory and visual hallucinations, paranoid delusions, self-abusive behaviors, and irritability) between 1 and 6 week after the switch to generic clozapine. Additionally, six patients exhibited mild exacerbations (i.e., reemergence or intensification of delusional ideation and idiosyncratic behaviors) [14].

One case report indicates increased paranoid delusions in patients a month after the switch to generic clozapine. His mental state stabilized 2 months after reintroduction of the reference drug [15].

Clinical outcomes after the conversion to generic clozapine were also assessed by evaluation of needs for medical services. No significant differences in inpatient hospital days, crisis center admissions, or outpatient psychiatric visits were observed in the retrospective study of 108 patients switched to generic clozapine [16].

The numbers of physician or therapist visits, hospitalizations, or emergency room visits were not significantly different between the 6-month period before and after the switch to generic clozapine in a study of 58 patients conducted by Alessi-Severini et al. [17].

Generic drug dose adjustment

The need for a dose adjustment after the conversion to a generic drug is considered an important measure of its therapeutic equivalence to the reference drug. In the study by Healy et al. [16] out of 108 patients, 16 patients required an increase, 11 a reduction, and 75 did not require any change in the dose of generic clozapine during a 1-year observation. On the other hand, no differences in clozapine doses after the switch to generic clozapine were reported in the study conducted by Sajbel et al. [18] and only one out of 24 patients needed a dose increase in the study by Stoner [10]. However, there was a significant increase in the dose of prescribed generic, compared to reference clozapine, in the study published by Kluznik et al. [9]. The necessity to increase the dose of generic clozapine was shown to be dependent on the duration of treatment with reference clozapine before the switch. Specifically, a significant dose increase was necessary only in patients treated for less than 18 months, whereas no significant dose adjustment was needed in patients treated for longer periods [11]. In the study by Alessi-Severini et al. dose changes assessed in 58 patients 2, 4, and 6 months after the switch to generic clozapine have been shown to be not statistically significant. In a half-year observational period, only six patients required a dose adjustment (4 patients required a dose increase and 2 patients a dose decrease) [17].

Safety profiles of reference and generic clozapine

Clozapine is known to negatively affect hematological parameters, and particularly white blood cells (WBC), causing leucopenia and agranulocytopenia. Therefore, a majority of studies that examine safety profiles of clozapine use WBC count as the readout.

In study by Sajbel et al. [18] assessing WBC count in 16 patients switched from reference to generic clozapine, no significant difference was found in the period of 4 months. Moreover, there were no reports of WBC being lower than 3.8×10^3 mm^{-3}, or any other adverse effects for that matter, during the entire study period. Similarly, hematologic monitoring performed by Alessi-Severini et al. in the period of 6 months before and 6 months after the switch to generic clozapine, did not reveal any statistical differences [17].

While Stoner and colleagues [10] reported trends toward a decline in WBC count and an increase in the absolute neutrophil count after the conversion to generic clozapine, the effects were not statistically significant. Only one patient in that cohort experienced neutropenia during treatment with generic clozapine, but the same patient similarly responded to earlier treatment with reference clozapine [10].

Other undesirable effects

Alessi-Severini et al. [17] reported several adverse effects in response to treatment with both reference and generic clozapine, including, cases of hypersalivation, drowsiness/sedation, tremor/muscle spasm, insomnia, dizziness, and headache. However, the effects were similar in character and their number did not differ significantly 6 months before and 6 months after the switch.

Similarly, in the randomized, open-label, multiple dose, crossover study by Golden and Honigfeld [19], approximately two-thirds of patients treated with reference and generic clozapine experienced adverse effects during the entire 19-day observation period. In this patient cohort, the symptoms included tachycardia, tachypnoe, hypersalivation, hyperpyrexia, constipation, somnolence, increased sweating, and orthostatic hypotension. However, again there were no significant differences between groups treated with the reference, compared to the generic clozapine.

Our review has also identified one relevant case report. It describes a significant elevation (up to 3644 U/l) of creatine kinase (CK) in a patient treated for 6 days with generic clozapine, and normalization of CK levels after reintroduction of reference clozapine [20]. Serious adverse effect was also described in Stoner et al. study—a case of pulmonary embolism after the conversion to generic clozapine in a patient with portal vein hypertension, cirrhosis, and esophageal varices [10].

Other antipsychotics

Data available in the literature for other antipsychotic drugs bioequivalence is very limited. We have found and synthesized all reports available to date for olanzapine and risperidone. No reports on bioequivalence of other antipsychotics were found.

Olanzapine

Therapeutic equivalence of reference olanzapine and three generic olanzapine products was studied by Araszkiewicz et al. [21]. Three groups of patients were compared: (i) patients

prescribed reference olanzapine and continued on it; (ii) patients prescribed reference olanzapine and switched to generic olanzapine; and (iii) patients prescribed generic olanzapine from the start. During a 2-year follow-up, there were no significant differences in the dose of generic olanzapine prescribed to 25 patients who were switched from reference olanzapine. No patient requested a switch back to reference olanzapine, which might indicate a good tolerance of generic olanzapine. The number of relapses before and after the switch was not significantly different, and the average number of relapses per year was equal. Both groups treated with only one drug throughout the observation period showed similar percentages of patients with relapses (reference olanzapine: 38%, generic olanzapine: 34%). The switched group showed the lowest average number of patients relapsing per year (12%), and again the numbers were similar in two groups without the switch (reference olanzapine: 24%, generic olanzapine: 26%) [21].

A case of mental state deterioration 2 days after switching to generic olanzapine was described by Samuel et al. [22] in a 14-year-old patient with bipolar affective disorder, childhood autism, and moderate mental retardation. Symptoms included an increased agitation, aggression, reduced sleep, and disinhibition. Increasing the dose of generic olanzapine was not effective in alleviating the symptoms. Notably, patient's mental state improved within 1–2 days after restarting brand-name olanzapine, strongly suggesting that the deterioration was indeed related to the switch to the generic form of the drug [22].

There are only single case reports of adverse effects of treatment with generic olanzapine. These include a case of akathisia 5 days after switching to generic olanzapine that resolved 48 h after resuming the branded drug, [23] and a case of gray tooth discoloration after few weeks of generic olanzapine treatment [24].

Risperidone

We have identified two reports describing cases of mental state deterioration after switching from reference to generic risperidone. First describes worsening of behavior, including hyperactivity and irritability, 2 weeks after the switch in a 6-year-old patient with autism and a severe intellectual disability, who had been stable for over 6 months. After reinitiation of reference risperidone, the patient significantly improved within 10 days [25].

The second report describes a case of an increased tiredness and sedation a few days after switching from reference to generic risperidone in a 14-year-old patient with paranoid schizophrenia. Within a week of reintroducing reference risperidone, the previously experienced side-effects disappeared, indicating a causal relationship between the symptoms and the generic [25].

Antidepressant drugs

Fluoxetine

A case of depressive symptom deterioration (i.e., sleeping difficulties and feeling sad) 16 days after switching to generic fluoxetine has been described in a patient suffering for 5 years from major depression (three episodes) and treated with reference fluoxetine. The patient was subsequently switched to reference fluoxetine administered twice-weekly, which relieved all the symptoms of depression in 2 weeks [26].

Another study describes depressive symptom deterioration with suicidal thoughts several months after switching to generic fluoxetine in a patient with a recurrent major depressive disorder treated for 2 years with reference fluoxetine. Four weeks after reintroduction of reference drug, the patient reported improvements in the mood, drive, concentration, and disappearance of suicidal thoughts. The patient remained free of symptoms for a 12-month follow-up period [27].

A similar case describes depressive symptom reoccurrence 18 days after switching to a generic fluoxetine in a patient treated for 2 years with the reference fluoxetine. Two weeks after reintroduction of the reference fluoxetine, the patient became again symptom-free [28].

Six cases of either adverse effects (i.e., moderate to severe headaches) or a decreased efficacy of generic fluoxetine (i.e., exacerbation of self-injurious behaviors, depression, anxiety, and fatigue, along with anhedonia, lack of concentration, lethargy, dysphoria, irritability, crying spells, isolation, and dampened motivation and energy) have been described in patients who had used reference fluoxetine for over a year before the switch [29].

Citalopram

The analysis of 172 patients with anxiety disorders (obsessive-compulsive disorder, panic disorder with agoraphobia, social phobia, posttraumatic stress disorder) treated with the reference citalopram, performed by Van Ameringen and colleagues has shown that 20 patients (12%) deteriorated after the switch to generic citalopram. Specifically, the reemerging or worsening clinical symptoms included suicidal ideation, increases in obsessive thoughts or compulsions, anxiety, panic attacks, restlessness, and mood lability. All 20 patients responded well to reintroduction of reference citalopram, but two of them needed a dose increase. Ten out of the 20 patients were concomitantly treated with other medications. However, their doses remained unchanged throughout the study [30].

Mirtazapine

There is one case report describing depressive symptom deterioration with suicidal ideation without life stressor a few weeks after switching from reference to generic mirtazapine in a patient who suffered from a major depressive disorder and obsessive-compulsive disorder, simultaneously treated with bupropion, imipramine, and diazepam [27].

Venlafaxine

A case of deterioration of depressive symptoms with suicidal thoughts was described 3 months after the switch to the generic venlafaxine in a patient who had previously been treated with the reference venlafaxine. After reintroducing reference venlafaxine, improvement of clinical state was noted [31].

Discussion

We conducted a systematic literature review in order to gain insights into potential changes in the therapeutic effectiveness as a result of a conversion from reference to generic forms of antipsychotic and antidepressive medicines.

Most of the available literature concerns efficacy and safety of generic clozapine. Even though the pharmacokinetic profile of generic clozapine meets the overall regulatory requirements, isolated cases of its decreased efficacy have nonetheless been described in the literature, and analyzed here. These cases may have likely been caused by the patient-to-patient variability in responsiveness to clozapine. But it is also well established that a pharmacological treatment may change both the sensitivity and the number of target receptors. The latter phenomenon, referred to as down- or up-regulation, may be responsible for the observed changes in the patient's mental state and for the need of a dose adjustment. Since changes in the sensitivity of target receptors are usually dependent on the duration of treatment, this factor should be included in future study designs.

Deterioration of clinical state after the switch could be caused by a decrease in concentration of the active substance in the

plasma, in turn leading to appearance of withdrawal symptoms. After a long-term treatment with antipsychotics, discontinuation syndromes can produce psychiatric symptoms that can be mistaken for a true relapse of the disease. The drug-induced effect is known as "supersensitivity psychosis"[32]. It can occur within 6 weeks following either a decrease or a complete withdrawal of an oral antipsychotic [33]. It can be distinguished from the relapse of the disease as the patient's clinical state improves more quickly after increasing the dose or readministration of the antipsychotic.

Equally important contributors to the therapeutic inequivalence of various forms of antipsychotic drugs may be individual differences in drug pharmacokinetics, which depends on P-glycoprotein, a well-established restrictor of the blood-brain barrier permeability. The gene encoding P-glycoprotein is highly polymorphic, leading to differences in the relationship between peripheral and central nervous system (CNS) levels of antipsychotic drugs among individuals [34]. Moreover, it is not known whether chronic antipsychotic or antidepressive treatment causes modulation of P-glycoprotein function, or its concentration in the CNS. If so, this could be yet another reason for the observed differences in the therapeutic response to the "reference → generic" antipsychotic drug switch.

Clozapine pharmacokinetics can change also by a simultaneous treatment with drugs that affect its metabolism through an inhibition or induction of hepatic cytochrome P450 (CYP) isozymes. Similarly, a 5-day caffeine-free period or a sudden smoking cessation can cause a significant decrease or an elevation of clozapine plasma concentration, respectively [35–37]. Unlike clozapine, only few case reports and one full study refer to therapeutic equivalence of other antipsychotic drugs—olanzapine and risperidone. It is worth emphasizing that, although some cases of impaired efficacy after conversion to generic olanzapine have been described, the switch does not seem to cause any increase in the number of adverse effects or change in their characteristics.

Non-pharmacological or not exclusively pharmacological factors are of major importance. An impaired compliance, often resulting in discontinuation of treatment, is one of the main problems faced by psychiatric pharmacotherapy [38,39]. While acceptable by regulations, any change in the size, shape, or color of the generic drug pharmaceutical form (e.g., tablet, capsule) may raise patient's concerns on the effectiveness of the therapy. This, in turn, may affect compliance, leading even to abandonment of the therapy. It may also cause the nocebo effect, resulting in a decreased effectiveness of the generic drug and the resultant clinical state deterioration [40–42]. Cai et al. describe a case of the lack of treatment effectiveness due to reluctance to use a generic product by a patient treated with venlafaxine [31]. Explaining to the patient the reasons for the change, and reassuring him/her about the similarity in action of different products containing the same active substance, may be critical to the success of treatment with generic drugs.

Clinical implications

Our systematic review revealed that changes in efficacy and adverse effects of treatment with generic antipsychotic and antidepressive drugs are rare, especially considering the large scale of this type of treatment administered daily. However, as reasons for these rare phenomena remain unknown and impossible to predict in individual cases, it seems that a careful clinical patient monitoring should be performed during at least the first few weeks after the conversion. In case of any mental state deterioration, psychological factors and the resulting decreased compliance should be considered and discussed with the patient. A dose adjustment of a newly introduced generic drug may be required as well. It should also be considered that a change in the clinical state experienced by the patient may result from psychological factors (i.e., the nocebo effect) and a fluctuation in symptoms as part of a natural course of the disease, not related to the generic drug.

It is worth noting that no study or a case report included data on switching between generics. No such data are available because generic drug bioequivalence is assessed only in relation to reference drugs. Switches between generics can be performed in pharmacy without doctor's knowledge [43]. For example, according to Polish regulations, pharmacists are obligated to offer to a patient a more affordable generic. Moreover, there are several generics of each reference drug available on the market, but not in every pharmacy. This also leads to switching between generics at the pharmacist's discretion. Even though the data shown by Davit et al. indicate that the differences in pharmacokinetic parameters among generics are not expected to exceed their acceptable ranges, doctors should be aware of the potential for disturbances in the therapeutic response [44].

If serious adverse effects or deterioration of the mental state occur, reference treatment should be reintroduced [45]. Manufacturing defects of certain batches of drugs, although happening very rarely, should also be considered as a possible reason for any decreased treatment effectiveness. All these situations should be reported to the relevant authorities. Such reports are carefully investigated and corrective actions are taken if necessary. As clinical studies comparing the efficacy and safety of "reference → generic" or "generic → generic" drug switches are ethically unacceptable, the available data should be considered incomplete. All cases of a therapeutic inequivalence should be carefully monitored and made available to the public. Medical professionals should be encouraged to publish observations associated with the drug switch in their own patients. Until a more complete set of data is available, all patients undergoing a drug switch should be carefully observed.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

None.

Acknowledgments

The authors express their gratitude to Dr. Agnieszka Bałkowiec for her thoughtful reading of the manuscript and helpful comments. This project has been realized with the use of the CePT infrastructure that had been financed from the European Union funds – European Regional Development Fund, Innovative Economy Programme 2007–2013.

References

[1] Kumar GP, Shekhar S, Rishi K. Hatch Waxman Act and generic drugs: a review. J Pharm Biomed Sci 2011;8:1–6.
[2] Rawlins M. Generic prescribing: unfinished business. Lancet 2015;385:219.
[3] Bałkowiec-Iskra E, Cessak G, Kuzawińska O, Sejbuk-Rozbicka K, Rokita K, Mirowska-Guzel D. Regulatory and clinical aspects of psychotropic medicinal products bioequivalence. Eur Neuropsychopharmacol 2015;25:1027–34.
[4] Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, Patel DT, et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug.Administration. Ann Pharmacother 2009;43:1583–97.
[5] US FDA. Clozapine in vivo bioequivalence and in vitro dissolution testing; 2005, http://www.fda.gov/OHRMS/DOCKETS/98fr/2003d-0549-gdl0002.pdf 30.12.2014.

[6] Pokorny R, Finkel MJ, Robinson WT. Normal volunteers should not be used for bioavailability or bioequivalence studies of clozapine. Pharm Res 1994;11:1221.
[7] Ford N, Hoen E. Generic medicines are not substandard medicines. Lancet 2002;359:1351.
[8] Hamann J, Mendel R, Kissling W, Leucht S. Psychiatrists' decision making between branded and generic drugs. Eur Neuropsychopharmacol 2011;23: 686–90.
[9] Kluznik JC, Walbek NH, Farnsworth MG, Melstrom K. Clinical effects of a randomized switch of patients from Clozaril to generic clozapine. J Clin Psychiatry 2001;62:14–7.
[10] Stoner SC, Lea JW, Dubisar B, Marken PA, Ramlatchman LV, Reynolds J. A program to convert patients from trade-name to generic clozapine. Pharmacotherapy 2003;23:806–10.
[11] Paton C. Generic clozapine: outcomes after switching formulations. Br J Psychiatry 2006;189:184–5.
[12] Makela EH, Cutlip WD, Stevenson JM, Weimer JM, Abdallah ES, Akhtar RS, et al. Branded versus generic clozapine for treatment of schizophrenia. Ann Pharmacother 2003;37:350–3.
[13] Oluboka O, Stewart S, Landry S, Adams S. Does therapeutic equivalence follow bioequivalence? A randomized trial to assess clinical effects after switching from Clozaril to generic clozapine (Gen-Clozapine). J Clin Pharmacol 2010;50:531–5.
[14] Mofsen R, Balter J. Case reports of the reemergence of psychotic symptoms after conversion from brand-name clozapine to a generic formulation. Clin Ther 2001;23:1720–31.
[15] Alvarez CA, Mascarenas C, Timmerman I. Increasing psychosis in a patient switched from Clozaril to generic clozapine. Am J Psychiatry 2006;163:746.
[16] Healy DJ, Taylor S, Goldman M, Barry K, Blow F, Milner KK. Clinical equivalence of generic clozapine. Community Ment Health J 2005;41:393–8.
[17] Alessi-Severini S, Honcharik PL, Simpson KD, Eleff MK, Collins DM. Evaluation of an interchangeability switch in patients treated with clozapine: a retrospective review. J Clin Psychiatry 2006;67:1047–54.
[18] Sajbel TA, Carter GW, Wiley RB. Converting Patients from brand-name clozapine to generic clozapine. Ann Pharmacother 2001;35:281–4.
[19] Golden G, Honigfeld G. Bioequivalence of clozapine orally disintegrating 100-mg tablets compared with clozapine solid oral 100mg tablets after multiple doses in patients with schizophrenia. Clin Drug Investig 2008;28:231–9.
[20] Schennach-Wolff R, Stubner S, Riedel M, Muller N. Extensive elevation of creatine kinase with generic clozapine, but not with Leponex. Psychiatry Res 2010;176:93.
[21] Araszkiewicz A, Szabert K, Godman B, Wladysiuk M, Barbuli C, Haycox A. Generic olanzapine: health authority opportunity or nightmare? Expert Rev Pharmacoecon Outcomes Res 2008;8:549–55.
[22] Samuel R, Attard A, Kyriakopoulos M. Mental state deterioration after switching from brand-name to generic olanzapine in an adolescent with bipolar affective disorder, autism and intellectual disability: a case study. BMC Psychiatry 2013;13:244–6.
[23] Goldberg JF. A case of akathisia after switching form branded to generic high-dose olanzapine. J Clin Psychiatry 2012;73:4.
[24] Galarneau D. A case of teeth discoloration upon transition from zyprexa to generic olanzapine. Ochsner J 2013;13:550–2.
[25] Hardan AY, Fung LK, Amin H. Risperidone: switching form brand name to generic. J Child Adolesc Psychopharmacol 2010;20:457–8.
[26] Shields BJ, Nahata MC. Efficacy of brand-name vs generic fluoxetine. Perspect Psychiatr Care 2003;39:134–5 (Letter to Editor).
[27] Margolese HC, Wolf Y, Desmarais JE, Beauclair L. Loss of response after switching from brand name to generic formulations: three cases and a discussion of key clinical considerations when switching. Int Clin Psychopharmacol 2010;25:180–2.
[28] Albrecht J. Therapeutic inadequacy in spite of bioequivaleny on replacing Fluctine with Fluocim. Swiss Med Wkly 2001;131:84.
[29] Yu BP, Chong YS, Maguire GA. Is generic fluoxetine effective? J Affect Disord 2004;81:185–6.
[30] Van Ameringen M, Mancini C, Patterson B, Bennett M. Symptom relapse following switch from Celexa to generic citalopram: an anxiety disorders case series. J Psychopharmacol 2007;21:472–6.
[31] Cai J, Fei C, Xu F. Impact of brand-name drug worship and expectation psychology on antidepressant efficacy. Int J Clin Exp Med 2013;6:724–6.
[32] Moncrieff J. Why is it so difficult to stop psychiatric drug treatment? It may be nothing to do with the original problem. Med Hypotheses 2006;67:517–23.
[33] Chouinard G, Choinard VA. Atypical antipsychotics: CATIE study, drug – induced movement dis order and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndrome. Psychother Psychosom 2008;77:69–77.
[34] Teh LK, Lee WL, Amir J, Salleh MZ, Ismail R. Single step PCR for detection of alleli variation of MDR1 gene (P-glycoprotein) among three ethnic groups in Malaysia. J Clin Pharm Ther 2007;32:313–9.
[35] Carrillo JA, Herraiz AG, Ramos SI, Benítez J. Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. J Clin Psychopharmacol 1998;18:311–6.
[36] Lowe EJ, Ackman ML. Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment. Ann Pharmacother 2010;44:727–32.
[37] Gage SH, Munafo MR. Rethinking the association between smoking and schizophrenia. Lancet Psych 2015;2:118–9.
[38] Friemann K, Wciórka J. Four measures of treatment compliance among patients recovering from psychotic episodes – a comparative study. Psychiatr Pol 2013;47:759–73.
[39] Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–23.
[40] Grabowski J, Bidzan L. Neurobiological expression of the placebo effect. Psychiatr Pol 2010;44:221–34.
[41] Bobo WV, Stovall JA, Knostman M, Koestner J, Shelton C. Converting from brand-name to generic clozapine: a review of effectiveness and tolerability data. Am J Health Syst Pharm 2010;67:27–37.
[42] Desmarais JE, Beauclair L, Margolese HC. Switching from brand-name to generic psychotropic medications: a literature review. CNS Neurosci Ther 2011;7:750–60.
[43] Cessak G, Rokita K, Bałkowiec-Iskra E. Bioequivalence and therapeutic equivalence of psychotropic drugs. Adv Psych Neurol 2015;24:8–17.
[44] Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, Patel DT, et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother 2009;43:1583–97.
[45] Carbon M, Correl CU. Rational use of generic psychotropic drugs. CNS Drugs 2013;27:353–65.