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REVIEW ARTICLE

Rational Use of Generic Psychotropic Drugs

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Abstract For economic reasons, the generic substitution of branded medications is common and welcome. These replacements are based on the concept of bioequivalence, which is considered equal to therapeutic equivalence. Regulatory standards for bioequivalence require the 90 % confidence intervals of group averages of pharmacokinetic measures of a generic and the original drug to overlap within ±20 %. However, therapeutic equivalence has been challenged for several psychotropic agents by retrospective studies and case reports. To evaluate the degree of bioequivalence and therapeutic equivalence of branded and generic psychotropic drugs, we performed an electronic search (from database inception until 24 May 2012 and without language restrictions) in PubMed/MEDLINE, Cochrane Library, and Web of Science. Search terms were "(generic) AND (psychotropic OR psychoactive OR antipsychotic OR antiepileptic OR antidepressant OR stimulant OR benzodiazepine)" or the respective individual substances. We included clinical studies, regardless of design, comparing branded with generic psychotropic drug formulations, identifying 35 such studies. We also included case reports/series reporting on outcomes after a switch between brand and generic psychotropics, identifying 145 clinical cases. Bioequivalence studies in healthy controls or animals, in-vitro studies, and health economics studies without medical information were excluded. An overview of the few randomized controlled studies supports that US FDA regulations assure clinically adequate drug delivery in the majority of patients switched from brand to generic. However, with a growing number of competing generic products for one substance, and growing economic pressure to substitute with the currently cheapest generic, frequent generic-generic switches, often unbeknownst to prescribing clinicians, raise concerns, particularly for antiepileptics/mood stabilizers. Generic-generic switches may vary by more than ±20 % from each other in individual patients since the pharmacokinetic properties of each generic may differ from the innovator drug in opposing directions. Ideally, therapeutic equivalence studies in addition to pharmacokinetic equivalence studies would be performed for each generic, reflecting the full variability of clinical responses due to changes of pharmacokinetic properties related to age, sex, ethnicity, genetic factors, and body mass index. This is particularly relevant, as bioequivalence studies are based on single-dose studies in healthy controls who are likely not representative of the patients who are prescribed the psychotropic medications. Additionally, individual case reports suggest potential clinical effects during brand-generic switches. Knowledge and consideration of intra-individual variations can help guide the clinical management during brand-generic or generic-generic switch periods. To optimize outcomes, clinicians need to consider that when using generic psychotropic medications, a change in the patient's

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clinical status can be related to psychological, interactional, physiological, and pharmacological factors that may or may not be related to the change to a generic drug. In addition, throughout all treatment periods, clinicians need to be aware of the currently dispensed product (i.e., branded or exact generic formulation), particularly when evaluating clinical changes in efficacy, tolerability, and adherence. If clinical problems occur, the first response should be an assessment of adherence and a careful dose adjustments of the generic drug rather than an immediate switch back to the originator.

1 Introduction

According to the Generics Pharmaceutical Association, $250 billion was saved in the US by the use of generic medications for the CNS alone in 1999–2008 [1]. Cost-effective treatment is particularly important in patients with psychiatric disorders because they often begin earlier in life, are chronic, and require life-long treatment. Nevertheless, reduced medication costs achieved by brand-generic switches or switches to the currently cheapest generic may be offset by the costs of relapse due to potential therapeutic inferiority or loss of compliance [2]. The US FDA regulations assure that non-branded products contain the exact same molecule and that this molecule reaches the bloodstream in a near-identical concentration as the innovator in healthy volunteers. Nevertheless, clinical reports of therapeutic failure and adverse events during switches to generic medications continue to clash with this impeccable concept. Moreover, the recent withdrawal of a generic version of bupropion extended release, 5 years after an initial series of complaints, illustrates the need for clinicians to be vigilant of potential clinical problems of generic psychotropic medications, not only during the early post-marketing period, but also throughout their clinical use. In this article, we discuss the available database, examining clinical aspects of the use of generic psychotropic medications, and suggest improving the use of generics in psychiatry through conscious management of potential individual pharmacokinetic differences that may have clinical effects.

We performed an electronic search (from database inception until 24 May 2012) in PubMed/MEDLINE, Cochrane Library, and Web of Science without language or time restrictions. Search terms were "(generic) AND (psychotropic OR psychoactive OR antipsychotic OR antiepileptic OR antidepressant OR stimulant OR benzodiazepine)" or the respective individual substances. We included studies comparing branded with generic formulations of psychotropic drugs regardless of design, identifying 35 such clinical studies. We also included case reports and case series reporting on outcomes after a switch between branded and generic psychotropic formulations, identifying 145 clinical cases. Bioequivalence studies in healthy controls or animals, in-vitro studies, as well as health economics studies without medical information were not included. Furthermore, due to the presence of more well-controlled studies with antiepileptics, case reports of antiepileptics used for seizure disorders were not systematically evaluated, but rather more emphasis was placed on the results of the controlled studies. Moreover, the FDA website was searched for regulatory information on generics. According to the recommendations of the National Cancer Institute [3], studies were graded based on the level of the quality of their design in descending order of strength, ranging from 1 = randomized controlled clinical trials (1.i. double-blinded; 1.ii. non-blinded treatment delivery) and 2 = nonrandomized controlled clinical trials (including subset and post-hoc analyses of randomized controlled trials) to 3 = case series (3.i. population-based, consecutive series, 3.ii. consecutive cases (not population-based), 3.iii. nonconsecutive cases).

In the following, we first summarize general information regarding all generics and next proceed to provide medication class-specific and substance-specific information; all information is derived from published literature and web searches as detailed above.

2 Pharmacokinetic Aspects of Generic Drugs

The FDA states [4]: "Any generic drug modeled after a single, brand name drug (the reference) must perform approximately the same in the body as the brand name drug. There will always be a slight, but not medically important, level of natural variability…." In accordance with WHO guidelines, the variability is defined by pharmacokinetic measures derived from single-dose studies in healthy controls with minimally 24–36 subjects [5, 6]. A generic medication is considered bioequivalent with the original product if the 90 % confidence intervals (CIs) of pharmacokinetic measures (i.e., mean area under the curve of the serum concentration time curve [AUC] and of the peak plasma concentration [C_{max}]) of the originator and generic overlap within ±20 % (since the inverse of 80 % is 125 %, the log transformed upper range is often given as 125 %). A 90 % CI is not designed to predict the likelihood of an individual value; rather the 90 % CI gives a prediction of the expected population mean of the next experimental group. Thus, a variation of the range of data through individual outliers is still possible. Indeed, a theoretical study simulating individual AUC variations due to brand-generic switches found that 6 % of patients can be expected to experience clinically meaningful changes in

AUC values [7]. Moreover, the bioequivalence studies in healthy controls receiving one single dose may not be fully representative of the variability in patients' age, gender, ethnicity, body mass index (BMI), physical health, smoking status, steady-state treatment, or comedication(s). Indeed, demographic data from bioequivalence studies of antiepileptics showed that participants were typically male (78.7 %) and Caucasian (54.4 %); only 0.71 % were elderly (>65 years) [8].

Since the FDA definitions of bioequivalence as a proxy for therapeutic equivalence have been challenged, particularly for substances with a narrow therapeutic index (NTI drugs), in 2011 the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at the FDA proposed to revise regulations for NTI drugs [9]. According to this proposal, future applications for generics of NTI drugs would have to include the use of a two-treatment, four-period, crossover design and an overlap of pharmacokinetic measures within the 95–105 % window [9].

In general, individual pharmacokinetic changes during a switch from a branded to a generic psychotropic medication are highly unlikely but possible in select subjects, which may result in the emergence of dose-related side effects for agents with higher absorption, or in diminished efficacy for agents with lower absorption. While these concerns have partly been supported by the retrospective studies and case reports reviewed below, prospective clinical studies addressing these concerns in larger groups systematically are missing for most psychotropic drugs.

3 Non-Pharmacokinetic Aspects of Generic Drugs

In addition to pharmacokinetic reasons for a maintained or changed clinical outcome after replacing a branded with a generic medication, other reasons need to be considered too. These reasons can be subdivided into biological and psychological factors.

The biological aspects of therapeutic in-equivalence may relate to the use of different inactive substances, e.g., carrier substances, sweeteners, or preservatives in specific generic vs. originator formulations. "Inactive" components underlie FDA regulations with safety testing prior to approval [10], and generic manufacturers typically refer to an existing repertoire of approved inactive components to combine these with their active ingredient. Nevertheless, for individual, unexpected clinical outcomes, the possibility of effects of inactive components is one variable worth considering, particularly in patients with pre-existing allergies, gluten or lactose intolerance [11]. Caution in psychiatric patients may also be appropriate when switching to products containing aspartame because of its alleged potential to aggravate mood symptoms in this population [12].

Non-pharmacokinetic factors, relating to psychological, attitudinal, and behavioral aspects, also need to be considered during the switch to and use of generics (Table 1). Such attention will support medication adherence, which is a key component for optimal outcomes, especially in psychiatry [13]. Indeed, a questionnaire-based study revealed considerable reluctance toward generic antipsychotics in patients with psychoses [14]. Adherence in patients receiving selective serotonin-reuptake inhibitors (SSRIs) was lowest in those taking the generic formulation [15]. Moreover, it has been suggested that changes of color, shape, and packaging of medications can even be conceptualized as maltreatment and poisoning attempts by some psychotic patients [16].

4 Data on Clinical Equivalence of Generic Drugs from Case Reports, Retrospective Data Base Studies, and Prospective Clinical Studies

Below is a summary of clinical studies comparing branded and generic formulations (Table 2, [17–51]) and of case reports on clinical observations related to generic psychotropic drugs (Table 3, [52–54]).

However, when evaluating the published evidence, one needs to bear in mind that, as described above, multiple factors can influence maintained or fluctuating efficacy, or the emergence of new or more bothersome side effects after a switch from a branded to a generic medication. Moreover, one also needs to bear in mind that reporting of clinical observations depends on the awareness of a potential clinical problem; thus, non-reporting does not necessarily reflect the absence of clinical effects. Furthermore, it needs to be stressed that there is significant heterogeneity of the quality of data sources between medication classes. Double-blind crossover studies, which are the best methodology to investigate this question, are almost entirely absent in psychopharmacology, except for clozapine.

4.1 Clinical Equivalence of Antiepileptics

Major concerns among all centrally active drugs have involved generic antiepileptics [55]. Notably, these concerns refer to their use in epilepsy, as antiepileptics are known to have a narrow individual therapeutic window. However, newer antiepileptics are most frequently used in elderly patients and for mood or pain disorders [56]. A review of case reports [52] provides an overview of clinical problems of switches from branded to generic antiepileptics with reports of increased seizure frequencies, significant changes in drug blood levels, increased likelihood of hospitalization, relapse of mood symptoms, or increased

Table 1 Non-pharmacokinetic aspects of switches from branded to generic medication

Possible mechanism	Outcome	
	No change	Worsening
Psychological[a]	Trust or indifference	Anxiety
Attitudinal[a]	Expectation of equivalence or superiority	Expectation of inferiority
	Adherence unaffected	Worsened adherence due to new appearance, shape, color or taste of the pill
Pharmacokinetic	Sufficiently similar bioequivalence	Insufficiently similar bioequivalence
	Sufficiently small difference in absorption, distribution, metabolism, or elimination due to non-active drug carrier substance(s)	Sufficiently large difference in absorption, distribution, metabolism, or elimination due to non-active drug carrier substance(s)
	Sufficiently small difference in area under the curve of the serum concentration time curve and/or the ratio of the peak plasma concentration between the branded and the generic drug	Sufficiently large difference in area under the curve of the serum concentration time curve and/or the ratio of the peak plasma concentration between the branded and the generic drug
Changes of inactive substance to:		
Aspartame	–	Panic attacks, mood changes, visual hallucinations, manic episodes, and isolated dizziness
Lactose	–	Abdominal symptoms in lactose intolerant subjects
Sorbitol, mannitol	–	>3 g/day, laxative effect
Parabens, methanol	–	Hypersensitivity reactions, urticaria
Propylenglycol	–	Possibility of toxic effects with ingestion of >25 mg/kg/day in adults, with cardiovascular, renal and CNS effects

[a] Pertaining to the patient, family member and/or prescriber

frequency of neurological and gastrointestinal side effects. Likewise, retrospective studies reported higher frequencies of adverse events and higher medical resource utilization with switches from branded to generic antiepileptics (Table 2, [23–25, 28–30, 32–36]). Importantly, however, retrospective studies are not blinded and are thus likely to be biased by attitudinal factors, such as the expectation of inferiority of the generic product, or worsened adherence with the generic. Particularly the results of open studies into resource utilization during the use of generic products may reflect patients' uncertainty regarding the therapeutic efficacy of the generic product, rather than true product differences. In this regard, prospective, blinded studies are more informative, but currently sparse. To date, only 171 patients were included in six randomized, controlled, blinded studies of antiepileptics (Table 2, [17–20, 26, 27]). In summary, these studies confirmed therapeutic equivalence of generic and branded antiepileptics, although they may be underpowered to detect differences in specific clinical subgroups [55]. Similarly, two recent meta-analyses of these studies showed comparable odds for seizure frequencies [57, 58]. There was also no increased likelihood of adverse events during generic treatment [57].

Due to the multitude of generics per active substance, switches among generics are common, but have rarely been assessed in clinical studies [22, 57]. Devine et al. [59], used data from a commercial health claims database and included 34,216 stable epilepsy patient files covering up to 12 months in a retrospective case-control study. They found a significantly increased risk (odds ratio (OR) = 1.51, 95 % CI 1.29–1.76) for seizures leading to hospitalization within 3 months of switching between FDA-approved (A-rated) generic antiepileptics. However, after adjusting for complex risk profiles, this finding was no longer significant. Interestingly, these risk factors included measures of comorbidity and polypharmacy. While the authors conclude that "an absence of effect [of switching] cannot be ruled out," one could also argue that this study confirms the clinical impression that particularly those with high comorbidity and titrated to polypharmacy are sensitive to the switch effects. Another case-crossover study using a health database found that refills even from the same manufacturer contributed to the risk of seizures and that the additional factor of switching among generics contributed only a marginal extra risk [35], yet lack of careful adherence measurement limits the interpretability of these results. Krauss et al. [8] addressed the shortage of clinical data in a study using data from bioequivalence studies of antiepileptics submitted to the FDA. They modeled 595 pairs of generic-to-generic switches and found that the vast majority of generic-to-generic combinations would be expected to fall within FDA-accepted

Table 2 Therapeutic efficacy and safety in clinical studies of generics versus branded antiepileptics, antipsychotics and antidepressants (summarized by design)

Substance	No. of studies	Study design	Total *N*	Level of evidence	Specific study results	Mean observation period
Antiepileptics						
Carbamazepine [17–20]	4	Randomized double-blind crossover studies	91	Level 1.i	No clinical differences in 3 out of the 4 studies Significantly increased rates of neurological adverse reactions in 1 study [19] ($n = 23$) in patients on generics	2–6 months
Carbamazepine [21, 22]	2	Prospective open-label crossover studies	38	Level 2	No significant differences in seizure frequencies; sequential tests of brand and 3 generics; one patient with signs of toxicity during generic but not during brand treatment period	9 days
Lamotrigine [23, 24]	2	Retrospective cohort studies	1,813	Level 3.i	Higher doses of generic lamotrigine needed, higher medical resource utilization in patients on generics (epilepsy only)	6 months
Lamotrigine [25]	1	Retrospective cohort crossover study	616	Level 3.i	No significant increase in adverse events, measured in ED visits, hospitalizations, and changes in comedication in a mixed cohort of lamotrigine users including 295 psychiatric patients	4 months
Phenytoin [26]	1	Randomized double-blind study	60 randomized to 4 arms: (1 brand, 3 generics)	Level 1.i	No significant difference in seizure frequencies	3 months
Phenytoin [27]	1	Randomized double blind crossover study	20	Level 1.i	Trough concentration differences of brand versus generic product	n.a.
Phenytoin [28]	1	Retrospective observational study	222	Level 3.iii	No significant difference in seizure frequencies during pre- versus postswitch intervals	6 months
Topiramate [29, 30]	2	Retrospective cohort studies of Canadian insurance databases	2112	Level 3.i	Increased use of additional AEDs with generic. Longer duration of hospitalizations and higher rates of additional prescription drug use	6 months
Valproic acid [31]	1	Prospective open-label crossover study	64	Level 2	No significant difference in seizure frequencies, no differences in plasma levels	4 weeks
Multiple AEDs [32] Carbamazepine; $n = 9{,}928$ Gabapentin; $n = 4{,}076$ Phenytoin; $n = 16{,}668$ Primidone; $n = 1{,}652$ Zonisamide; $n = 1{,}301$	1	Retrospective open-label cohort study (health insurance database)	33,625; 8,468 with psychiatric comorbidity	Level 3.i	Significant differences during generic use periods: Higher risk of injury, higher use of other prescription drugs, increased rates of all-cause hospitalization, epilepsy-rated hospitalization and outpatient services. Increased duration of hospitalization	4 years
Multiple AEDs [33, 34] Carbamazepine, Gabapentin, Phenytoin, Primidone, Zonisamide, Clonazepam, Ethosuccimid, Valproate, Lamotrigine	2	Retrospective case-control studies of health claims databases	1,407	Level 3.i.	Higher rates of antiepileptic polypharmacy with generic, higher rates of hospitalizations with generics	5 months

Table 2 continued

Substance	No. of studies	Study design	Total *N*	Level of evidence	Specific study results	Mean observation period
Multiple AEDs [35] Carbamazepine, Clonazepam, Gabapentin, Phenytoin, Lamotrigine, Valproate, Clobazam, Topiramate	1	Retrospective case crossover study of health claims database	1,762	Level 3.i	Slightly increased (4–19 %) seizure-related events during switch periods	3–4 weeks
Multiple AEDs [36] Phenytoin; $n = 1{,}490$ Valproate; $n = 1{,}652$ Lamotrigine; $n = 1{,}301$	1	Retrospective case-control study of a health claims database for Medicare and commercial plans of patients in the USA	4,278	Level 3.i	Increased rates of prescription changes (i.e., discontinuation, dose changes, adding another AED) during phenytoin generic treatment No other clinical differences, no change in hospitalizations or ED visits	
Antipsychotics						
Chlorpromazine [37]	1	Randomized double-blind	54	Level 1.i	No clinical differences	
Clozapine [38]	1	Randomized double-blind two-period crossover study	45	Level 1.i	Worsening of CGI and BPRS (mean) during generic phases Improved BDI during generic phases Increased rate of "relapses" in the generic group (with relapse described as marked anxiety and insomnia, and increase in positive psychotic symptoms).	5 months
Clozapine [39]	1	Randomized double-blind switch study	39	Level 1.i	No significant pre- or postswitch difference in CGI or side effect measures	6 months
Clozapine [40–46]	7	Prospective observational switch studies	553	Level 3.ii	Majority of patients showed no clinical worsening, no increased rate of relapses after switches	6–12 months
Clozapine [47–49]	3	Retrospective chart review studies	366	Level 3.iii	No significant differences in outcome parameters (i.e., service utilization in 2 studies and CGI scores in 1 study)	2 weeks–12 months
Clozapine [50]	1	Pharmacokinetic study in schizophrenia patients stabilized on Clozaril®	21	Level 3.ii	Significantly lower C_{max} with generic. Total drug delivery (AUC) fell below 80 % of original in 24 % of subjects during generic treatment	n.a.
Antidepressant						
Fluoxetine [51]	1	Randomized, double-blind crossover study	40	Level 1.i	No significant differences in safety and efficacy at 6 months At week 12: lower clinical antidepressive efficacy in generic Increased side effect rates in generic (anxiety, diarrhea)	6 months

ED emergency department, *na* not applicable, *AEDs* antiepileptic drugs, *BDI* Beck Depression Inventory, *BPRS* Brief Psychiatric Rating Scale, *CGI* Clinical Global Impression, $AUC_{0\text{-}t}$ Total drug delivery, C_{max} Maximum concentration, *CK* creatine kinase

According to the recommendations of the National Cancer Institute [3], studies were graded based on the level of the quality of their design in descending order of strength, ranging from 1 = randomized controlled clinical trials (1.i. double-blinded; 1.ii. non-blinded treatment delivery) and 2 = non-randomized controlled clinical trials (including subset and post-hoc analyses of randomized controlled trials) to 3 = case series (3.i. population-based, consecutive series, 3.ii. consecutive cases (not population-based), 3.iii. nonconsecutive cases

Table 3 Overview of published case reports on switching between branded and generic psychotropic drugs (except for antiepileptics used for epilepsy). Adapted from Desmarais et al. [52]

Generic	Reported clinical issues related to switching from innovator to generic		Number of cases reported
	Possible increased drug delivery	Possible decreased drug delivery	
Antipsychotics			
Clozapine	Excessive CK elevation [30] ($n = 1$)	Psychotic relapses ($n = 8$)	9
Olanzapine	New-onset akathisia and dystonia [31]	–	1
Risperidone	Increased sedation ($n = 1$)	Worsening of behavioral problems and psychosis ($n = 2$)	3
Thioridazine	Increased side effects ($n = 2$)	Clinical detoriation ($n = 1$)	3
Antidepressants			
Amitriptyline	–	Worsening of depression, agitation	2
Bupropion; extended release	Increased side effects ($n = 7$)	Worsening of depression ($n = 78$)	85
Citalopram	Increased side effects ($n = 8$)	Re-emergence of depression ($n = 24$)	24[a]
Desipramine	Increased side effects	Worsening of depression	1[a]
Fluoxetine		Worsening of depression	6
		Relapse of obsessive-compulsive disorder	1
Mirtazapine		Worsening of depression	1
Nortriptyline	Intoxication		1
Paroxetine		Re-emergence of anxiety and depression	2 (+1 case of loss of efficacy during generic-generic switch effect)
Sertraline	Unusual side effects, heat flush		1
Mood stabilizer			
Lithium		Insufficient plasma levels	2
Tranquilizer			
Alprazolam	Increased sedation		1
Clonazepam		Panic disorder relapse	1

[a] Individual cases with reported inefficacy plus potential intolerability symptoms

CK Creatine kinase

ranges of bioequivalence measures (the three lighter shades of orange in Fig. 1a for AUC and Fig. 1b for C_{max}). However, they also found that the total drug delivery would be expected to vary more than 15 % in 17 % of the simulated switch studies (dark orange areas in Fig. 1a). Expected switch-related variations in peak exposure were calculated to be >15 % in 39 % (dark orange areas in Fig. 1b); some combinations would even be expected to exceed a 25 % variation [8]. Variations likely leading to clinical effects [60] were found for valproic acid, Oxcarbazapine, gabapentin, topiramate, and zonisamide [8]. Another theoretical simulation of individual shifts of total drug delivery found that 12 % of patients were expected to experience clinically meaningful dose changes upon generic-generic switching [7]. On the other hand, a study analyzing European regulatory pharmacokinetic data for topiramate and gabapentin [61] did not find generic-to-generic combinations to vary exceedingly with regard to differences in C_{max} and AUC.

4.2 Clinical Equivalence of Antipsychotics

Generic first-generation antipsychotics (FGAs) have been in use for more than two decades with only very few reports on loss of efficacy or adverse events related to switching between branded and generic drugs. FGAs (Table 3, for review see [52]). However, several original FGAs (e.g., fluphenazine, oral haloperidol, perphenazine, thioridazine) have been completely replaced by their generic substitutes, such that current switches only happen between generics. The only available, double-blind study on the efficacy of branded vs. generic chlorpromazine confirmed their clinical equivalence (Table 2 [37]). Among all second-generation antipsychotics (SGAs), clozapine was the first that went off patent, but despite the long-term use of generic clozapine (since 1998 in the USA), some controversy remains about its pros and cons [62]. An early pharmacokinetic study in 21 schizophrenia patients, previously stabilized on branded clozapine and subsequently

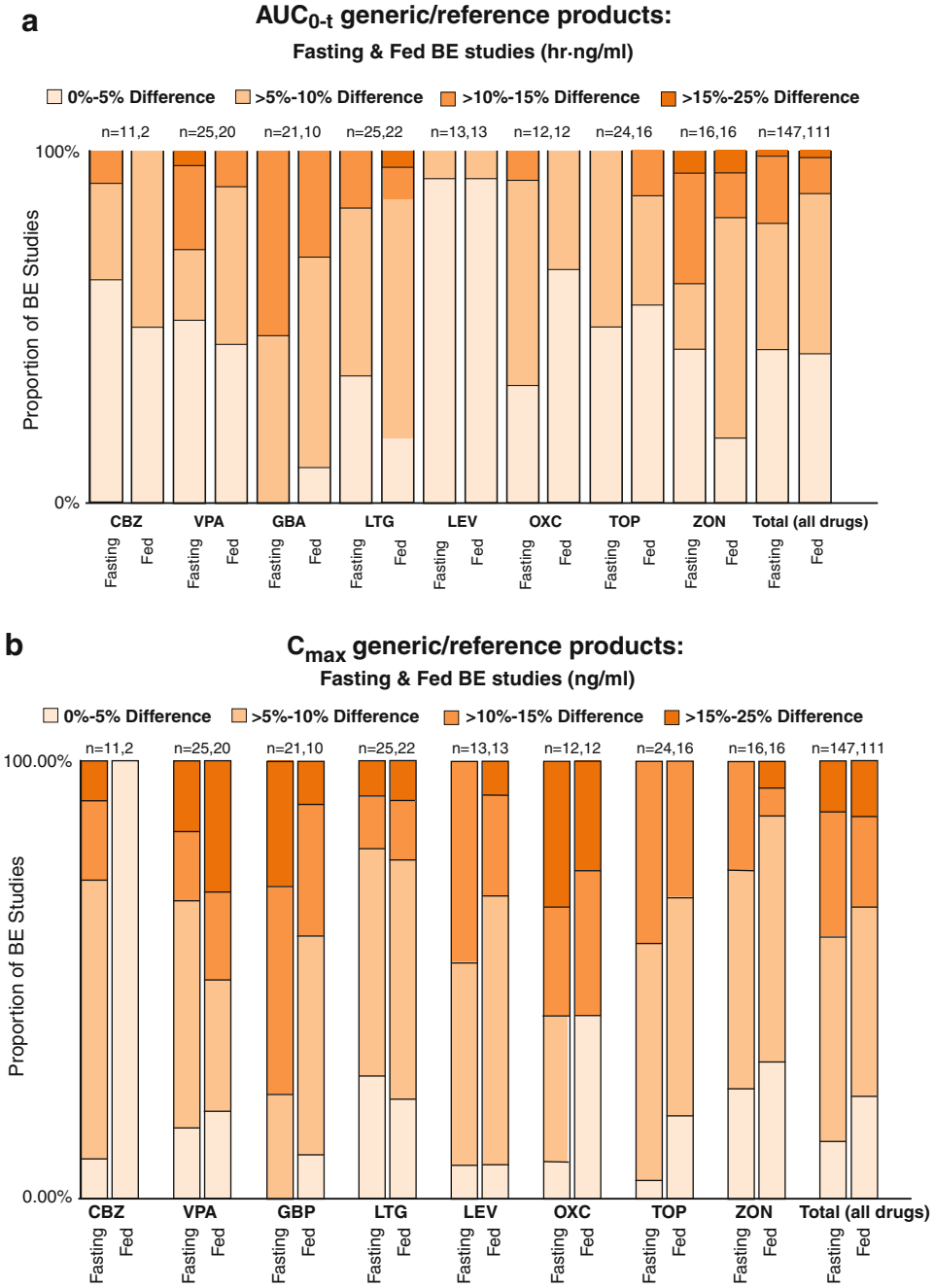

Fig. 1 Simulated switches between generic antiepileptics (reprinted with permission from Krauss et al. [8]). **a** Differences in 90 % confidence intervals for limits of total drug exposure (AUC_{0-t}) geometric mean ratios for generic and reference antiepileptics (AED) classified in 5 % increments. Proportions of fasting and fed BE study results are shown on the vertical axis. Nearly all AUC_{0-t} values differ by <15 %. **b** Differences in 90 % confidence intervals for peak concentration (C_{max}) geometric mean ratios for generic and reference AED formulations classified in 5 % increments. Proportions of fasting and fed BE study results are shown on the vertical axis. AED abbreviations: *CBZ* carbamazepine, *GBP* gabapentin, *LTG* lamotrigine, *LEV* levetiracetam, *OXC* oxcarbazepine, *TOP* topiramate, *VPA* divalproex, *ZON* zonisamide

switched to the generic counterpart, showed significantly lower peak plasma levels in 24 % of patients and a trend toward lower total drug levels (AUC) for the entire group [50]. Moreover, re-emergence of psychotic symptoms after switching from branded to generic clozapine was documented in several cases [52]. However, these older reports may be due to the fact that the FDA had granted a waiver to perform bioequivalence studies of clozapine in volunteers with very low doses. Currently, the FDA recommends a single-dose, two-treatment, two-period crossover in-vivo study with 100 mg tablets in patients treated with clozapine to test bioequivalence of branded and generic clozapine formulations [63].

While the majority of patients in open-label and retrospective chart studies did not experience any problems during/after switching to generic clozapine (Table 2, [40–49]), the only two randomized controlled studies reported opposite results (Table 2, [38, 39]). Kluznik et al. [38] performed a double-blind, two-period crossover study in 45 patients in a secure facility and found a worsening of Clinical Global Impression (CGI) and Brief Psychiatric Rating Scale (BPRS) during the 2-month generic periods.

They also described a higher proportion of clinical relapses in a post-hoc descriptive chart analysis, but these relapses had not been predefined as outcome criteria and were characterized qualitatively only by increased insomnia, anxiety, and positive symptoms. By contrast, Oluboka et al. [39] performed a randomized, double-blind crossover study in 39 stable patients with schizophrenia or schizoaffective disorder and reported full therapeutic equivalence with neither increases in adverse events nor clinical deteriorations. Notably, both studies found results in favor of their respective study sponsor.

As more and more SGAs are going off patent, it is important to be aware of the possibility of clinical changes in some individuals during brand-generic or generic-generic switch periods without spreading mistrust toward generics among patients. As generic risperidone and olanzapine have only been in use for a relatively short period and only in some countries, larger case series or controlled studies are missing. To date, the bioequivalence of one generic formulation of risperidone has been questioned, since only the pharmacokinetic parameters of metabolized 9-hydroxy-risperidone, but not of the parent compound, risperidone, fell within the required 80–125 % range [64]. Moreover, three cases of either clinical worsening or increase in adverse effects with a generic formulation of risperidone were published [65, 66], involving an elderly subject, an adolescent, and a child, i.e., subjects whose pharmacokinetic specifics may not be represented in bioequivalence studies of healthy adult volunteers. Similarly, only few reports concern generic olanzapine. The only existing retrospective chart review is highly limited, as relapses were not evaluated and numbers of adverse events were not analyzed [67].

4.3 Clinical Equivalence of Antidepressants

As with antipsychotics, few concerns have been raised regarding generic antidepressants. Generic tricyclic antidepressants have long been in use, but only three case reports described treatment failures and one intoxication associated with switches from branded to generic products (for review, see [52], Table 3). Notably, these cases all involved elderly subjects, who may be more sensitive to minimal pharmacokinetic variations. Despite shorter off-patent times, there are, however, more case reports of therapeutic non-equivalence of generic versus branded serotonin/noradrenaline (norepinephrine)-reuptake inhibitors. In these case reports, predominantly loss of efficacy was observed, but increased side effects were also noted that were not limited to patient groups in whom larger variations in pharmacokinetic effects would be expected. The only double-blind, crossover study comparing branded fluoxetine with its generic counterpart concluded that these drugs differed clinically during the initial treatment period, but remained published as a conference presentation only (Table 2, [51]).

During the early post-marketing period of generic extended-release bupropion in 2007, the clinical equivalence of these formulations was questioned by a series of 78 cases with loss of efficacy after switching from the branded to a generic version. In the subsequent re-evaluation of the pharmacokinetic studies, the FDA initially dismissed these clinical concerns [68], and no further reports on similar clinical problems were published in the medical literature or on the FDA website until October 2012. In October 2012, however, Teva withdrew Budeprion® XL 300 mg as FDA data had proven non-bioequivalence of this formulation. In line with the concept of bioavailability, the original approval of these 300 mg extended-release tablets had been based on data obtained in healthy controls after administration of the 150 mg tablet, because the administration of 300 mg tablets to healthy controls was deemed unacceptable due to the potential risk of seizures associated with bupropion. Although the official dismissal of concerns remained on the FDA website until September 2012, Teva had been asked by the FDA to study Budeprion® XL 300 mg in more detail soon after the registered complaints. The requested study was designed to include patients who had reported lack of efficacy after switching from Wellbutrin XL 300 mg to Budeprion® XL 300 mg [69]. However, the study failed because of recruitment problems. Subsequently, the FDA conducted a single-dose crossover bioavailability study in 24 healthy volunteers [70]. In that study, the generic, Budeprion® XL 300 mg, failed to fulfill bioequivalence criteria. The C_{max} of Budeprion® XL 300 mg was only 75 % of the innovator drug, and in select volunteers the AUC was less than 40 % of the innovator drug [70]. While the FDA acknowledges [70] that these data should have been obtained sooner after the complaints were submitted, the FDA's official position is that they "do not believe that the results of the FDA study should cause concern regarding the overall reliability of the agency's approval process for generic drugs, including the use of extrapolation [of dosages]."

4.4 Clinical Equivalence of Benzodiazepines

Various generic benzodiazepines have long been used, but there are only two published case reports on loss of efficacy with generic benzodiazepines (for review see [52], Table 3). It is unclear whether or not the absence of information reflects the absence of reported problems related to switches to or among benzodiazepine generics or whether there is a lack of reports because of a lack of awareness.

4.5 Clinical Equivalence of Psychostimulants

Of all psychotropic medications, different and complex delivery systems have been worked on and refined the most for methylphenidate and amphetamine salts, leading to at least 19 different formulations with highly specific pharmacokinetic properties [71]. While the various long-acting formulations are still patented, generic versions exist of the older, immediate-release formulations. There have been no reports of clinical problems related to switches among these products. Among the longer-acting stimulants, Methylin®-ER, Metadate®-ER, and Ritalin®-SR (sustained release) are therapeutically equivalent, although they use a different matrix for the delayed or sustained delivery. While no data seem to be available that question this equivalence, a lack of bioequivalence was found for two European extended-release formulations [72], particularly depending on the presence of concomitant food intake [73].

5 Generic-Generic Switches

Despite reassuring evidence regarding safe switches from a branded medication to a generic drug, the potential issues of switches between generic formulations remain entirely elusive in psychiatric patients. In accordance with substitution guidelines, pharmacists typically dispense the currently cheapest generic with each prescription, mostly without the knowledge of the prescribing clinician. Thus, the treating clinician may often be unaware of the specific, currently dispensed product. As each generic medication is tested only against the branded drug, but not against any other existing generic, pharmacokinetic parameters of generics that each comply with the maximum ±20% variation requirement against the branded formulation could have larger variability between each other, as shown for antiepileptics [8]. For example, risperidone oral solution is currently available from ten different generic manufacturers in the USA and olanzapine oral tablets from six different manufacturers in the USA [5]. Moreover, increasing globalized trade supports the purchase of non-FDA-approved generics. Indeed, some online pharmacies market counterfeit products not approved by the FDA that cannot be distinguished from the originator by lay persons [74]. Although drug re-import is illegal in the USA, the regions bordering Canada have seen organized drug shopping trips for the elderly with purchases of non-FDA-approved generics to save medication costs [75].

The availability of multiple FDA-approved generics is further complicated by the fact that drugs are being resold and repackaged from one company to a second (or third), such that the dispensed product cannot always be easily traced back to the manufacturer listed in the FDA's substitution list [5]. Pharmacists have recognized the complexity of this situation and have developed decision tools for the choice of substitutions [76]. However, the interdisciplinary cross-talk of treating clinicians and dispensing pharmacists remains underdeveloped.

6 Medico-legal Considerations

A New York Times article from 20 March 2012 [77] highlights court rulings based on a recent Supreme Court ruling, which liberated generic drug companies from responsibilities in law suits because of missing warnings on package inserts. According to the Supreme Court, the generic manufacturers cannot be sued for failing to alert patients about the risks of their drugs, as the package insert is copied from and updated by the originator manufacturer. If this remains the case, then prescribing generic medications could translate to depriving patients of the possibility to successfully sue a company in a medico-legal malpractice suit if that company is not the maker of the branded drug that determined the content of the package insert.

7 Summary and Conclusions

Generic psychotropic medications effectively reduce medication costs if used appropriately. Nevertheless, every single switch bears the possibility of altering the outcome in select patients. A change in the patient's clinical status can be related to psychological, interactional, physiological, and pharmacological factors that may or may not be related to the change to a generic drug. Thus, brand-generic and generic-generic switches should be clinically monitored, but without the a priori expectation of inferiority. Prescribers should evaluate and address any psychological and attitudinal barriers to the successful switch. In addition, throughout all periods of treatment, clinicians need to be aware of the currently dispensed product (i.e., branded or exact generic formulation), particularly when evaluating clinical changes in efficacy, tolerability, or adherence. If clinical problems occur, the first response should be a careful consideration of psychological, attitudinal, or adherence issues as well as of potential differences between formulations, including the comparison of excipients. As a next step, clinicians should consider a dose adjustment of the generic or a switch to another generic with well-tolerated excipients. However, frequent switches among generics should be discouraged. Only if these steps are unsuccessful should a switch back to the branded formulation be considered.

Ideally, the potential differences between branded and generic medications should be evaluated in clinical studies in sufficiently large cohorts of real-world patients as opposed to

healthy controls only. These studies also need to consider the effects of comedications, assess variations of the pharmacokinetic profile caused by drug-drug interactions, and include patients with a broad representation of age groups, ethnicity, and BMI. A more complete understanding of the relationship between medication plasma concentration and clinical response (gained in studies with the original drug) will also be important to understand and predict the full impact of potential differences in pharmacokinetic measures of innovator and generic products. Finally, the regulatory requirements for narrower pharmacokinetic equivalency, as proposed for NTI drugs, such as antiepileptics, may need to be expanded to medications in which relationships between plasma levels and therapeutic or adverse effects are less clear. With tighter regulatory constraints of the bioequivalence of a generic compared with a branded drug in healthy volunteer studies, clinicians and patients would have, at least, greater assurance that the seemingly same medication has the desired, sufficiently similar biological activity.

Until more definitive data are available, it is important to raise the awareness among clinicians that not all medications containing the same active pharmacological ingredient have exactly the same biological activity. Whether or not any of these differences actually have clinical importance will need to be assessed as part of the clinical care of the patient that needs to take into account the actually dispensed medication and whether and how it is taken. Greater awareness of all of these factors is hoped to improve patient care.

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