

Generic antidepressant drugs: a reappraisal

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Introduction

Generic drugs are lower-cost versions of brand-name medications for which the patent has expired. Generic products have the same active ingredient as the brand-name drug, but can be marketed at a lower price, as their manufacturers are not influenced by the costs of the original registration studies. The reduction of health care costs is a high priority for governments of many countries in the industrialized world, and the introduction of generic drugs involves remarkable savings. The Generics Pharmaceutical Association estimated a \$250 billion saving in the US alone by the use of CNS generic medications in the period from 1999-2008 (IMS MIDAS, 2009).

Although generic formulations are less expensive than the corresponding brand-name drugs, it is debated if they are as safe or effective (Carbon and Correll, 2013). Controversies have sometimes arisen regarding generic substitution, and there is concern among some physicians and patients that brand-name drugs may be clinically superior to generic drugs. This issue is particularly relevant in some therapeutic areas such as psychiatry where special consideration is needed before switching a patient to a generic alternative. Many psychotropic agents currently in use are available as generic products. With regard to antidepressants, the number of generic formulations has increased steadily in the last few years in Italy. Despite evidence of cost savings, anecdotal reports and uncontrolled studies have described relapses

and worsening clinical outcome as well as adverse effects in patients after a switch from a branded to a generic formulation of antidepressants (Desmerais et al., 2011; Carbon and Correll, 2013). Moreover, a generic formulation of bupropion extended-release has been recently withdrawn from US market, 5 years after an initial series of complaints (Woodcock et al., 2012). Overall, these considerations have contributed to generating widespread negative perception and opposition, among physicians and patients, concerning the use of generic products in depression.

The aim of this article is to review general issues on generic drugs and their branded versions, with particular regard to antidepressant drugs.

The approval process for generic drugs: bioequivalence and clinical equivalence

When patents for brand-name medications expire, usually 10 to 20 years after registration, generic drugs with the same active ingredients may become available. According to regulatory agencies in the United States (Food and Drug Administration-FDA) and European Union (European Medicines Agency-EMA), a generic drug must be identical or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use (Food and Drug Administration, 2002; Committee for medicinal products for human use, 2010). Criticism of the use of generic drugs often refers to the

process of approving generic medications, which is not as rigorous as for the original drugs. In fact, unlike branded drugs, generic medications are not required by regulatory agencies to undergo efficacy and safety studies before being marketed (Kummet and Gelenberg, 2005). For the approval of a generic formulation, manufacturers must demonstrate an "essential similarity" between the candidate drug and the brand-name medication. Compared with the original medication, the generic drug must have the same amount and type of active ingredient, same route of administration and the same therapeutic effectiveness, as demonstrated by a bioequivalence study (Borgherini, 2003). Therefore, companies developing generic medications do not have to prove therapeutic equivalence, which would require further efficacy and safety studies, and the product must simply pass a test of bioequivalence. In other words, based on the criteria of regulatory agencies, if two formulations are bioequivalent, they are assumed to be similarly effective and safe.

Bioequivalence is a pharmacokinetic concept that compares the bioavailabilities of drugs. Bioavailability is defined as the fraction of an administered dose of unchanged drug that reaches systemic circulation. Two products are considered to be bioequivalent when they are administered at the same molar dose, under similar conditions in an appropriately designed study that demonstrates similar bioavailability. Specifically, according to drug regulatory agencies, the bioequivalence of a generic

drug compared with the brand-name counterpart should be demonstrated by a standardized, single-dose, cross-over pharmacokinetic study that is conducted in 24-36 healthy volunteers. Following administration of the dose, two pharmacokinetic parameters, namely area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}), are measured for both drugs. Bioequivalence is then established when the 90% confidence intervals for the ratios of the generic to the reference compound for the AUC and C_{max} fall within a 0.80 to 1.25 range (*or are within the interval from 80% to 125%*) (Borgherini, 2003; Blier, 2009).

Whether bioequivalence reflects clinical equivalence is controversial. Indeed, there are some important limitations of the current requirements for bioequivalence. First of all, based on the previously defined regulatory standards for bioequivalence, two different generics of the same compound can theoretically have up to 45% difference in AUC and C_{max} ratios (Yim 2009). While such pharmacokinetic variations are not significant in most cases, they can become important with drugs with a narrow therapeutic index or nonlinear kinetics (Borgherini, 2003). Under these circumstances, even small changes in serum concentration may lead to loss of therapeutic effect or even toxicity. Moreover, the delicate balance achieved in polypharmacy may be disrupted by a formulation change in medications that may induce or inhibit hepatic drug-metabolizing enzymes such as anticonvulsants (Crawford et al., 2006) and antidepressants (Spina et al., 2008). Another important limitation is related to the design of bioequivalence studies. These are usually small, cross-over trials, conducted in healthy volunteers, mostly young men, non-smokers and not taking other medications. Therefore, data from bioequivalence studies do not take into account the

possibility of variation due to gender, age, environmental factors and comorbid medical illness (Meibohm et al., 2002; Crawford et al., 2006; Blier, 2007; Shi et al., 2008). Furthermore, single doses do not reproduce real-life situations as target plasma concentrations are unlikely reached. Ideally, bioequivalence and pharmacokinetic studies should be performed in both patients and healthy controls (Cutler, 2001).

In addition to pharmacokinetic reasons for a changed clinical outcome after replacing a branded with a generic medication, other aspects including biological and psychological factors need to be considered (Carbon and Correll, 2013). Concerning biological aspects, generic and brand-name medications have the same type and quantity of active compounds but may contain different excipients including preservatives, pH adjusters, antioxidants, thickening agents, buffers and substances to adjust tonicity (Borgherini, 2003). In a 2001 draft guideline for industry, the US Office of Generic Drugs addressed the problem of impurities that may occur in the manufacture of generic drugs (Food and Drug Administration 2002a). Despite the lack of specific regulations concerning the excipients in a generic formulation, these substances cannot be considered inactive or inert molecules (Davies, 2001). For example, switching to products containing aspartate has been associated with worsening of mood symptoms in psychiatric patients (Walton et al., 1993). Psychological, attitudinal and behavioural aspects should also be taken into account when switching to generic drugs, especially in psychiatric patients. With regard to this, a recent survey examining psychiatrists' attitudes in choosing between branded or generic antidepressants and antipsychotics reported a relatively low willingness to use generic drugs (Hamann et al., 2013). Moreover, changes in shape, colour,

taste and packaging of the generic medication towards the originator may affect adherence to treatment. Indeed, in a study in patients with major depressive disorder, Liu et al. (2001) found that adherence and persistence to treatment were higher in subjects treated with three branded antidepressants, namely duloxetine, venlafaxine and escitalopram, than in those receiving generic selective serotonin reuptake inhibitors (SSRIs).

Generic antidepressants: economic implications and switch-related therapeutic failure/adverse effects

Most antidepressants currently in use are now available as generic formulations. At the time of preparation of this manuscript, the only antidepressants still patent-protected in Italy are escitalopram, duloxetine, bupropion and agomelatine.

Generic antidepressants should generally offer significant prescription drug cost savings compared with brand-name medications. However, some case reports and bioequivalence studies suggest a disadvantage in efficacy and tolerability of generic medications versus brand-name equivalents.

Economic implications

Cost-effective treatment is particularly important in patients with psychiatric disorders requiring chronic, life-long treatment. As part of containing the rising cost of health care, managed care organizations are increasingly adopting intervention programs designed to encourage efficient use of pharmaceuticals including generic step therapy (Gleason, 2007). Step-therapy programs require the use of first-line medications, usually lower-cost generic drugs, prior to receiving coverage for a second-line agent, usually a branded product. As the value of branded over generic anti-

depressants has not been unequivocally demonstrated, generic products may offer cost savings without an increase in adverse health outcomes. Studies examining the economic implications of generic antidepressant step-therapy programs have produced mixed findings (Panzer et al., 2005; Dunn et al., 2006). Panzer et al. (2005) developed a model estimating total medical and pharmacy costs associated with a generic step therapy (GST) formulary compared with an open formulary for selective serotonin reuptake inhibitors (SSRI) in a hypothetical health plan with 1,000,000 members. In this model, the frequency of therapy change and early treatment discontinuation were considerably greater for the GST formulary than for the open formulary, resulting in an overall medical cost increase to a health plan, despite a reduction in pharmacy costs. On the other hand, Dunn et al. (2006) showed that a step-therapy requiring patients to use a generic antidepressant prior to use of a brand-name medication resulted in consistent drug cost savings in the first year of implementation of the program.

To date, only a few studies have investigated the economic impact of use of generic antidepressant drugs. Wade et al. (2010) compared the total annual healthcare expenditure per patient associated with 12 months use of branded escitalopram, generic SSRIs and branded venlafaxine in patients with severe depression. The use of generic SSRI was found to involve significant savings compared with branded venlafaxine, but not with branded escitalopram. A recent investigation examined discontinuation rates and healthcare costs comparing patients who initiated antidepressant therapy with generic versus brand-name SSRI or SNRI (Vlahiotis et al., 2011). The adjusted comparison suggested that there was no significant difference in the likelihood of discontinuation between patients who started therapy with generic or

brand-name antidepressants. On the other hand, the analysis of healthcare costs indicated that costs were lower among patients starting a generic antidepressant compared with those starting a brand-name drug. A study performed on 4449 patients with major depressive disorder found that, compared with patients who continued on their patented SSRIs, patients who switched to a generic SSRI incurred more resource use of hospitalizations/emergency department visits and higher disease-related healthcare costs over a 6-month period (Wu, 2011).

Based on these data, the effects of generic substitution of antidepressants should be carefully examined, since use of generic alternatives may not be a cost-saving strategy when total healthcare costs are considered. Nevertheless, the reduced medication costs obtained by brand-generic switches may be counterbalanced by the costs of relapse due to possible therapeutic inferiority or loss of compliance.

Switch-related therapeutic failure/adverse effects

Although the use of generic antidepressants may result in substantial savings in prescription drug costs, it is still debated if they are always as safe or effective than the corresponding brand-name medications. In this respect, a number of published case reports have documented the occurrence of clinical deterioration or adverse effects following generic substitution (Desmerais et al., 2011; Carbon and Correll, 2013). In addition, some pharmacokinetic studies failed to show bioequivalence between generic and brand-name antidepressants.

Tricyclic antidepressants

Generic tricyclic antidepressants have long been used, but only three case reports have described treatment failures and one intoxica-

tion associated with switching from branded to generic products (Desmarais et al., 2011). Ostroff and Docherty (1978) described a 56-year-old man with depression controlled with amitriptyline 150 mg/day. Symptoms of depression reappeared when amitriptyline was switched to a generic formulation, and dosage was subsequently increased to 250 mg/day. Blood levels were found to be higher with 150 mg of the first formulation than with 250 mg of the second. The return to the branded amitriptyline formulation was associated to improvement of depression. Schnur (1995) reported cessation of agitation in an elderly patient when generic amitriptyline was changed to a brand formulation. Moreover, he also described a 97-year-old patient who developed anorexia, depression and lethargy on generic desipramine. When the medication was changed to the brand-name medication at the same dose, the patient became alert, oriented and cheerful. A case of severe nortriptyline intoxication was reported by Dubovsky (1987) when a patient was unknowingly changed from a generic to brand-name formulation. Notably, these cases all involved elderly subjects, who may be more sensitive to minimal pharmacokinetic variations.

Selective Serotonin Reuptake Inhibitors (SSRI)/Serotonin and Noradrenaline Reuptake Inhibitors (SNRI)

Despite shorter off-patent times, there are more case reports of therapeutic non-equivalence of generic versus branded newer antidepressants including selective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI). In these case reports, predominantly loss of efficacy was observed, but increased side effects were also noted. However, non-reporting does not necessarily reflect the absence of clinical effects, since

the reporting of clinical observations strictly depends on the awareness of a potential clinical problem.

The only randomized, double-blind, crossover study comparing a branded antidepressant with its generic counterpart involved fluoxetine (Bakish, 2000). While during the initial treatment period (at week 12) generic fluoxetine was associated with a lower antidepressant effect and increased rates of side effects (anxiety and diarrhoea) than original fluoxetine, no significant differences in safety and efficacy were observed at 6 months. However, this contribution remained published as a conference presentation only. Three cases of relapse of depression (Albrecht and Adler, 2001; Shields and Nahata, 2003; Margolese et al. 2010) and a case of relapse of obsessive-compulsive disorder (Hovaguimian, 1998) were described following generic substitution of fluoxetine. In all cases, patients improved after returning to the original medication. In two other cases, patients experienced allergic reactions to generic fluoxetine but not to the brand-name formulation (Baumann and Kahn, 2003). Yu et al. (2004) reported on six patients where a switch from branded to generic fluoxetine was associated with worsening of depressive symptoms and/or increased side effects. Both patients improved once their original medication was reinstated. Van Ameringen et al. (2007) described the re-emergence of symptoms or development of new adverse events in 20 patients with anxiety disorders when they were unknowingly switched from brand-name citalopram to one of its generics. All patients improved following reinstatement of their brand-name medication. Rosenthal et al. (2008) described seven patients who had an increase in symptoms or a relapse after a change in the formulation of their antidepressants. Six patients had been switched from branded paroxetine or citalopram to a generic formulation, whereas one had

been switched from one generic paroxetine to another. Miller (2007) described a patient switched from original sertraline to a generic formulation who developed transient warmth and flushing every time he took the medication. Side effects subsided when the dose of generic sertraline was lowered. Switch-induced symptoms of depression and suicidal ideation were also described in a 47-year-old woman following mirtazapine substitution (Margolese et al., 2010).

A crossover study compared the pharmacokinetic profiles of brand name and generic formulation of citalopram and venlafaxine extended-release on two groups of healthy male volunteers each (Chenu et al., 2009). Generic citalopram formulation appeared to be bioequivalent to the original, as the 90% CI for the C_{max} ratio of generic to brand-citalopram was between 97% and 100%. Conversely, the generic formulation of venlafaxine extended-release was not bioequivalent to the original. Venlafaxine plasma levels were significantly higher in volunteers taking the generic formulation as opposed to brand-name. Volunteers on generic venlafaxine also experienced significantly more side effects. The average C_{max} ratio of generic to brand venlafaxine was 150% with a 90% CI of 104-217%, failing to meet standards of many regulatory agencies. Therefore, the venlafaxine generic formulation was found to release its ingredients more rapidly and outside the acceptable norm.

Bupropion

The recent withdrawal of a generic formulation of bupropion extended-release illustrates the need for clinicians to be vigilant of potential clinical problems of generic antidepressants, not only during the early post-marketing period, but also throughout their clinical use. The clinical equivalence of generic extended-release bupropion was questioned in 2007, during the early

post-marketing period, by a series of 78 cases with loss of efficacy and 7 cases with increased adverse effects after switching from the branded to a generic version. Improvement in side effects and depression was observed in more than half of patients who returned to the original medication. The FDA initially dismissed these clinical concerns (Food and Drug Administration, 2010), but then conducted a single-dose, crossover bioequivalence study in 24 healthy volunteers (Woodcock et al. 2012). The results of this investigation indicated that the generic 300 mg extended-release formulation marketed by Teva, failed to fulfil bioequivalence criteria. Indeed its C_{max} was only 75% of the innovator drug, and in select volunteers the AUC was less than 40% of the innovator drug. Therefore, in October 2012, Teva withdrew this formulation as the FDA data had proven its non-bioequivalence. Interestingly, the original approval had been based on data obtained in healthy controls after administration of the 150 mg tablet, which were then extrapolated to the 300-mg product. In fact, administration of 300 mg tablets to healthy volunteers was considered unacceptable due to the potential risk of seizures associated with bupropion.

Conclusion

The availability of generic antidepressants should be regarded as an opportunity to reduce expenditure on drug costs and deploy limited resources more widely and effectively. However, switching to a generic antidepressant may be associated with a loss in therapeutic response or increased adverse effects with corresponding reductions in medication adherence. Prospective studies of generic substitution in psychiatric patients are needed. In addition to pharmacokinetic bioequivalence studies, the potential differences between branded and generic antidepressants, as well

as other psychotropic medications, should be evaluated in clinical studies in sufficiently large cohorts of real-world patients as opposed to only healthy controls. These investigations should reflect the full variability of clinical response due to changes of the pharmacokinetic profile related to age, sex, ethnicity, genetic factors and comedications. Until more definite data are available, switching between different formulations of the same antidepressant should be considered on an individual basis. Clinicians and pharmacists should inform patients about the potential consequences of generic switches, and frequent switches among generics should be discouraged. Physicians who are aware that a brand-name antidepressant may be switched to a generic formulation should advise their patients to be vigilant for a reduction in therapeutic response or an increase in adverse effects. Patients who are seen for relapses or failure to respond as expected should bring their medication to the office visit so the physician can determine if this outcome may be related to switching from a brand-name to a generic product. The same situation could also occur if the pharmacy switched the patients from one generic drug to another. Brand-generic and generic-generic switches should be clinically monitored, but without the a priori expectation of inferiority. Ideally, clinicians should employ a program of regular clinical assessment upon generic antidepressant substitution. Changes in the patient's clinical status including therapeutic failure and/or adverse effects should then be reported to local pharmacovigilance centres (or units) and, subsequently, to national regulatory authorities.

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