The Ochsner Journal 13:550–552, 2013

A Case of Teeth Discoloration Upon Transition From Zyprexa to Generic Olanzapine

David Galarneau, MD

Department of Psychiatry, Ochsner Clinic Foundation, and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA

ABSTRACT

Background: Although crucial to the success of the US healthcare system, generic medication is not without some risks, especially when a transition is made midtreatment from a brand-name formulation to its generic counterpart. Thankfully, such a transition is usually orderly and unnoticed, without disruption to the treatment; however, this is not always the case.

Case Report: This case study details an example of 1 such unfortunate disruption to treatment. A stable patient with schizophrenia was switched from brand-name Zyprexa to generic olanzapine. Within several months of the switch, the patient suffered a marked grayish discoloration of his teeth. His medication regimen was then transitioned from generic olanzapine to a new but different brand-name medication (Abilify). The transition was a success, with resolution of the adverse effect and continued stability of his mental state.

Conclusion: Generic olanzapine was introduced to the market in fall 2011. It remains to be seen whether this adverse effect was simply an anomaly or the beginning of a more ominous trend.

INTRODUCTION

In an age of ballooning healthcare costs, inexpensive generic medication is a fact of life. Given the ubiquity of generics, these medications must be of high quality and reliability. For the most part they are, playing a pivotal role in our healthcare system and promoting a fair and competitive consumer market. However, it is crucial that physicians, pharmacists, and patients alike understand exactly what they are prescribing, dispensing, or ingesting.

Although they are fair approximations, generic medications are not indistinguishable from their brand-name progenitors. Generics are bioequivalents, not exact replicas of brand-name medications. The US Food and Drug Administration (FDA) designates a generic formulation therapeutically equivalent to the brand-name medication when it has "equivalent clinical effect and no difference in its potential for adverse effects."[1]

Under current FDA standards, bioequivalence is designated when a generic formulation differs, in terms of its rate and extent of absorption, by no less than 20% and no more than 25% of its brand-name progenitor.[2] Or, to be more specific, "two products are considered to be bioequivalent if the 90% clearance (Cl) of the relative mean Cmax, AUC(0-t), and AUC(0-∞) of the generic drug to the brand-name drug is within 80% to 125% in the fasting state."[1]

Notably missing from the designation of therapeutic equivalence are product packaging, scoring, configuration, shape, and pharmaceutical additives such as color, preservatives, and flavorings.[2] These additives, or inactive ingredients, are also known as excipients.[3] The FDA has approved more than 700 excipients that can be grouped into roughly 40 unique categories.[3]

Excipients are chosen to be biologically inert and nonreactive with the active ingredients, but patients nonetheless show differing responses to them, and such responses can unfortunately even extend to allergic reactions in some patients. Thus, the excipients, in addition to the active ingredient(s), are a common cause for findings of bioinequivalence between brand-name and some candidate generic formulations.[4]

Address correspondence to
David Galarneau, MD
Department of Psychiatry
Ochsner Clinic Foundation
1514 Jefferson Highway, BH-4
New Orleans, LA 70121
Tel: (504) 842-4025
Fax: (504) 842-6264
Email: dgalarneau@ochsner.org

Keywords: Drug toxicity, drugs—generic, psychotropic drugs

The author has no financial or proprietary interest in the subject matter of this article.

In the case of psychotropics, numerous examples of clinical problems arising from generic substitution have been reported.[5] Notable examples include clonazepam, valproic acid, carbamazepine, and chlorpromazine. Practitioners must be vigilant when working with special populations such as psychiatric patients because the disease process can sometimes impair their ability to effectively convey information to the physician.

The discovery and subsequent release of the atypical antipsychotics, beginning in the mid-1990s, was a considerable step forward in the evolution of psychotherapeutics. This class of medication, which includes olanzapine, has benefited countless patients, many of whom are the very sickest and most refractory of the psychiatric population. Another notable member of this class, risperidone, was the first to become available in a generic formulation in July 2008. Olanzapine followed with its release in October 2011. As generics for the rest of the class eventually become available, it remains to be seen how these formulations will match their brand-name counterparts. The following case study illustrates the potential for problems on the horizon.

CASE REPORT

A 30-year-old male with stable schizophrenia had been on low- to medium-dose brand-name Zyprexa for many years. Sometime in the late fall of 2011 when the patient filled his monthly prescription, the pharmacist dispensed generic olanzapine instead of Zyprexa. The patient's physician had not provided specific instructions not to use a generic medication if it became available.

Upon his return to the office in January 2012, the patient stated that his family wanted him to inform the physician that his teeth had become discolored in the period between appointments. The patient denied teeth discoloration previously while on brand-name Zyprexa. Examination of his teeth showed a marked change—a noticeable gray discoloration. No other adverse effects were noted, and the efficacy of the generic was similar to the efficacy of the brand-name drug. The patient was on no other medications and could think of no other reasons that might explain his teeth discoloration.

After discussing options, including switching back to brand-name Zyprexa, the patient requested a trial of a new medication. Abilify was selected, and a cross-taper was discussed. The patient returned for a follow-up appointment 1 month later. He continued to do well, with no significant change in symptomatology, and the discoloration of his teeth had largely faded; his teeth were approaching their original color.

The underlying mechanism leading to the patient's teeth discoloration remains open to speculation. Although causality cannot be assumed, it is certainly suggestive that the switch from brand-name Zyprexa to generic olanzapine was the reason for the graying of his teeth. This particular untoward effect is not a common reaction with brand-name Zyprexa, and no mention is made of it in the package insert supplied by the manufacturer Eli Lilly. Taking this information into account and given that the patient did not experience this side effect prior to the cross-taper, it seems likely that his reaction was secondary to one or more of the excipients in the generic formulation. A review of Eli Lilly's original Zyprexa patents reveals the following:

> Olanzapine, a potent compound showing promising activity for use in treating psychotic patients tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeneity of the finished solid formulation.
>
> Applicants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient conditions, at elevated temperatures, and by moist environments.
>
> Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.[6]

Given the intrinsically metastable nature of the active molecule olanzapine, novel excipients chosen for generic formulations could have the undesired side effect of discoloration. Whether this effect will lead to an increased incidence of teeth discoloration as it likely did in this patient remains to be seen.

CONCLUSION

Close monitoring will undoubtedly be required as more patients make the transition from brand-name Zyprexa to a generic formulation of olanzapine.

REFERENCES

1. U.S. Food and Drug Administration Center for Drug Evaluation and Research. *Approved Drug Products with Therapeutic Equivalence Evaluations*. 29th ed. Silver Spring, MD: U.S. Department of Health & Human Resources, 2009.
2. Weinberg MA. How is the quality of a generic drug evaluated? *US Pharm*. 2009;34(6)(*Generic Drug Review* suppl):31-38.

3. Brownlee CL. Adding that "spoonful of sugar" - and more. *Modern Drug Discovery*. 2002;5(5):34-36, 38.
4. Lamy PP. Generic equivalents: issues and concerns. *J Clin Pharmacol*. 1986 May-Jun;26(5):309-316.
5. Keen PJ. Innovative versus generic medicines. *J R Soc Med*. 1991 June;84(6):375-378.
6. Moris TC, Lang HJ. Innovative versus generic medicines. European Patent Application 0 830 858 A1; 1998.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.