

Generic News

When is a Generic a Bad Generic – and how can I keep the Pharmacy from switching Generics?

So when is a generic a bad generic? If you read this article I think we can demonstrated that the answer to this question is almost never and we offer tools to spot issues!

OK, we have all heard the story: “Doctor, this new generic pill is not working!” So what is the real story?

Well, to understand this tangled web we need to define some terms. First, generics are drugs that have the same active ingredient, strength, dosage form and route of administration as a brand medication.¹ Generic substitution is allowed by the FDA when drugs are “AB rated” – that’s code for “not much difference.” In such a case, the pharmacist can substitute the drug without telling the prescriber provided the prescriber has indicated that generic substitution is permitted on this kind of prescription. The Food and Drug Administration (FDA) bases evaluations of substitutability, or “therapeutic equivalence (TE),” on scientific evaluations. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand-name product and must produce blood levels similar to those of the brand name product. Drug products evaluated as “therapeutically equivalent” can be expected to have equal therapeutic effect – as well as no difference when substituted for the brand-name product. Generic manufacturers are held to the same batch-to-batch standards as are the brand drugs. Some of the criteria used include:

- Generics are pharmaceutical equivalents (contain the same active ingredient(s); dosage form and route of administration; and strength.)
- Generic drug companies must have an approved application that contains adequate scientific evidence through in vivo and/or in vitro studies the bioequivalence of the product to a selected reference -listed drug.
- All generic manufacturing, packaging and testing sites must pass the same quality standards as those of brand name drugs. Many generic drugs are made in the same plants as innovator brand name drug products.
- No in vivo bioequivalence issue can be known or suspected in generic’s active ingredients or dosage forms.

How do we reconcile these differences?

Kesselheim et al reviewed 38 published clinical trials that compared cardiovascular generic drugs to their brand-name counterparts. They found no clinical evidence that the brand-name heart drugs worked better than the generic heart drugs.¹ So what about drugs with a narrow therapeutic index? Kesselheim et al evaluated 16 studies (9 RCTs, 1 prospective nonrandomized trial, 6 observational studies) comparing brand-name and generic antiepileptic drugs (AED), in an effort to determine whether evidence suggests that brand-name drugs are better at maintaining seizure control over the generic equivalent. What Kesselheim and colleagues found was that the available evidence

does not suggest an association between loss of seizure control and generic substitution with at least three types of AEDs.

Consider this – there may be many issues operating and therefore the answer is complex. Perhaps combinations of factors are in play and therefore no one issue explains the problem. But, if we put some evidence together there may be some considerations to help you find a solution. Consider the following multiple possibilities.

- **Treatment failures do occur when taking generic or brand-name drugs.** The patient and the doctor are more likely to be paying closer attention to the patient's symptoms when the generic drug is substituted for the brand-name drug and may attribute the relapse to the generic drug rather than a relapse that would have occurred had the patient stayed on the brand-name drug.
 - **Differences in a client's metabolism may be an issue.** We do not know how ADHD drugs are metabolized in the blood by plasma proteins and PubMed returns no results "fast metabolizer" and stimulants. But, we do know that differences between patients in stimulant metabolism can vary as much as 10-30%.
 - **Compliance or adherence may be an issue.** Most patients only take their medications about 50% of the time. Typical reasons cited by patients included forgetfulness (30 percent), other priorities (16 percent), decision to omit doses (11 percent), and lack of information about the importance of the treatment (9 percent).⁴
 - **The placebo effect is stronger than you think.** Waber et al performed a randomized controlled study to look at the effectiveness of a placebo that cost \$2.50 compared to a placebo that costs only 10 cents. Waber found that the placebo priced at \$2.50 reduced pain 85.4% compared to 61.0% pain reduction with the 10 cent placebo. This implies that patients perceive the brand-name drug to work better only because it has a higher price.³ Therefore, improving the patient's perceived value of the generic drug may also result in better efficacy of the generic drug.
 - **Monthly switching of generics happened.** Some pharmacies change their generic supplier as often as monthly depending on who gives them the best price.
- So what's a prescriber to do?** How do we hold down costs and not reduce quality? Here are some suggestions:
- Prescribers should know whether their pharmacies routinely switch generics and who have stable sources. After all, would you refer your patients to a specialist who changed techniques without telling you?
 - Prescribers should counsel their clients to question the pharmacy when the color, size or packaging is different. Pharmacists are required by law to counsel on all prescriptions.
 - Prescribers should be aware of switching and can simply call the pharmacist, get the NDC number or manufacturer of the generic that worked, by the patient's account, and by writing this number on the script that particular generic can be ordered and maintained by the pharmacy. I've done it – it works.
 - Prescribers should not underestimate the placebo effect. Suggesting that a generic is inferior can plant a seed of concern in the patient's mind.

- Prescribers who rely on drugs with a narrow therapeutic index (e.g. anticoagulants, thyroid and seizure medications) should be aware of these issues and counsel their clients to ask the pharmacies for a stable generic manufacturer.
- Prescribers should always remember that non-compliance can also explain poor effectiveness. Don't jump to a "bad drug" conclusion too quickly.

So when is a generic like a brand?

I think we have demonstrated that the answer to this question is almost always. Generic drugs are not inherently inferior to brand-name drugs, many things may explain why a generic does not work as well in an individual patient as the brand-name drug did. Both generic and brand-name drugs are necessary to treat our clients appropriately, both are effective and both have a place in drug therapy and on a formulary or a preferred drug list.

Right now you may be saying to yourself that "this all sounds good on paper but do we really trust the bioequivalent process?" What about all those rumors that a generic drug can differ from the brand? You are not alone in asking these questions. Davit et al reviewed 2,070 human studies that compared the absorption of brand name drugs into a person's body relative to its generic counterpart.² These studies were submitted to the FDA to support the approval of generic drugs. Davit et al found that the average difference in absorption between the brand and the generic was only 3.5 percent. This amount of difference is expected and acceptable, for one batch of brand-name drugs tested against another batch of the *same* brand-name drug! When was the last time you heard about batch to batch variation in brand drugs?

We need generics and we need brand drugs. Both are effective, and both have a place on a script, formulary or a preferred drug list. We also need to be good stewards and use the least cost equally effective drugs.

1. Drugs@FDA Glossary of Terms, Page Last Updated: 01/07/2010, <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>. visited 8/3/2010
2. Davit 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(10):1583-97
3. Kesselheim et al. Clinical equivalence of generic and brand name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA.* 2008;300(21):2514-2526
4. Krueger, et al. Medication Adherence and persistence: A comprehensive review. *Advances in Therapy.* 2005;22(4):313-56
5. Waber, et al. Commercial features of placebo and therapeutic efficacy. *JAMA.* 2008;299(9):1016-17

II: Q&A FRIST, SOME NEW INFORMATION ON GENERIC ANTIPSYCHOTICS

What's up with "Generics First" in new antipsychotic (AAP) starts?

Our policy is to recommend a generic second generation atypical antipsychotic (AAP) for a first start client when an AAP is indicated. In general, there is no evidence available to help predict a selective response among these agents, so our policy is to use the most cost-effective medication first unless there is a cogent reason to do otherwise. Currently, the most cost-effective medication is generic Risperidone. Medicaid Purchasing Administration (MPA) will follow both medication pricing and evolving evidence concerning prediction models closely, and modify this policy as new information becomes available. By the way, this mirrors the policies of Western and Eastern state hospitals in caring for our more serious clients.

What are the guidelines around AAP new starts when the brand is a better choice?

- Use of another brand name atypical antipsychotic is actually a documented continuation therapy of what is a currently stable regimen (i.e. in claims and other sources).
- There has been a past trial of Risperidone that resulted in discontinuation due to side effects (e.g. per client's recollection).
- There has been a past trial of Risperidone that resulted in discontinuation due to lack of benefits (e.g. noted in a claim or clinical record).
- There is a history of hyper-prolactinemia or movement disorder (e.g. dystonic reaction or akathisia).
- When there are FDA indications not covered by Risperidone or another generic medication (e.g. bipolar with acute depression).
- Client requests another drug or refuses Risperidone and it is documented in the clinical record.
- EPA criteria will require good documentation in retrospective payment review.

II: Q&A

SOME NEW INFORMATION ON GENERIC ANTIPSYCHOTICS FIRST (continued)

Adult AAP generics and safety first – How do I get an emergency fill?

Can the client get an emergency fill?

Yes – Pharmacies are authorized to fill your prescription during off hours in an amount they deem clinically needed. They will be paid if reported within 72 hours.

Can the client get what is needed in a crisis?

Yes -- by writing on the script “Adult in Crisis” or indicating the need based on the “Generic First criteria above

Can the prescriber use samples as refill protections?

No. Why use samples if MPA pays for all drugs without co-pays, and why dispense a sample to a Medicaid client when the script is non-transparent to other prescribers, ERs and

Can the client continue on his or her existing meds?

Yes. These are not considered new starts

Will an emergency start be counted as a “refill protection?”

Yes

What defines new AAP start?

- Medicaid will look back 180 days and if there is a drug claim in the AAP class we continue therapy.
- Medicaid will have a low threshold to continuations by either prescriber or the client.

What is the cost difference?

For your consideration the Average Daily Cost (ADC) ratio of AAP brands range are 3 to 24 times more expensive than generic resperidone. The ADC is our cost per drug times your average prescription amounts made into a ratio by dividing each drug’s ADC by the lowest ADC to obtain a ratio.

Anti-psychotics: What does the Science Say about Brand and Generics AAPs?

Here is a brief summary of the science that supports our “Generics First” policy. The full OHSU technology report can be found at http://derp.ohsu.edu/final/AAP_final_report_update_23.pdf. Please remember your “Generics First” policy is for new starts or treatment naïve patient and therefore some science may not apply when comparing chronic longer term use (e.g. the CATIE trails).

Rate of discontinuation: Brand vs. Generic

Data from discontinuation rates from 67 head-to-head trials were used in a mixed treatment comparisons analysis. This analysis includes data from all phases of the CATIE study; with 1493 patients enrolled in Phase I this study constitutes the largest study among the 67 included in the analysis. The mixed treatment comparisons analysis uses both direct and indirect comparisons based on the head-to-head trials and found that olanzapine and clozapine are superior to aripiprazole, quetiapine, Risperidone, and ziprasidone in rates of all-cause discontinuation of assigned drug across all the trials. Additionally Risperidone and quetiapine were found to be superior to ziprasidone. A difference between clozapine and olanzapine was not found. This analysis controlled for between study heterogeneity and dose level within study (low, medium, or high) using the fixed-effects model.

It did not control for within study heterogeneity for those studies where there are more than two drug arms. Dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. For example, early studies of Risperidone often used doses well above those used today, and clozapine and olanzapine studies used doses below those used today. There are fewer data available for the newer drugs, particularly aripiprazole and paliperidone. Hence, results for these drugs should be interpreted with caution.

Antipsychotics, few studies provide comparative data across atypical antipsychotics for any one adverse event.

Tolerability and Adverse Events: Brand and Generic

The atypical antipsychotics have differing adverse event profiles, both in short- and long-term. Adverse events that are intolerable lead to discontinuation from studies, although some may take longer to result in discontinuation. Such discontinuations take into account the patient’s evaluation of the degree to which the adverse event is tolerable. The CATIE trials included these discontinuations as a secondary outcome measure and found statistically significant differences among the drugs. In CATIE Phase I, discontinuations due to adverse events were highest among patients taking olanzapine and lowest among those taking Risperidone).

Data from discontinuation rates from 67 head-to-head trials were used in a mixed treatment comparisons analysis. This analysis used direct and indirect comparisons based on the head-to-head trials and found that clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, quetiapine, or Risperidone. olanzapine resulted in such discontinuations significantly more often than quetiapine or Risperidone, and quetiapine had fewer discontinuations for adverse events than ziprasidone. As noted previously, dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. There are fewer data available for the newer drugs, particularly aripiprazole and paliperidone. Hence, results for these drugs should be interpreted with caution.