Generic Substitution of Narrow Therapeutic Index Drugs

By Mays Putrus

Controversy regarding generic substitution of narrow therapeutic index drugs, especially antiepileptic drugs, has become a big debate lately. Some states are considering passing laws that will restrict the generic substitution of these narrow therapeutic index drugs. In fact, some states have already modified their laws to limit switching and generic substitution of these medications, requiring patient and prescriber consent before the substitution is made. One of the precipitating factors that led to this debate occurred in 1997, and will be discussed later. Since this is a controversial topic, pharmacists are facing ethical dilemmas in dealing with these issues. Should the pharmacist generically substitute these narrow therapeutic index medications?

Pharmacists’ views are mixed regarding this issue. Some pharmacists argue against this regulation and say that the pharmacist has the clinical knowledge and appropriate skill to be able to make their own decisions about generic substitution of these medications, and that it should not be regulated. Other pharmacists argue for the regulation and think it will help protect patients and save money. I conducted a survey, and one of the issues I assessed was pharmacy students’ opinions regarding this matter. The results will be discussed later in the paper. Many new antiepileptic drugs will be going generic in the next few years, and pharmacists will have to face the decision of whether or not to generically substitute these medications.

Initiatives have been taken by some brand name manufacturers of these narrow therapeutic index products, in an attempt to distinguish them from the generic
counterparts, even though the FDA has concluded them to be therapeutically equivalent. These brand name manufacturers have characterized these medications as a unique class of drugs that deserve special attention and more rigorous bioequivalence standards. However, the FDA has rejected this notion and defends its standards as being sufficient for these drugs, as well as any others. Thus, some of these brand name manufacturers have lobbied and are currently lobbying for legislation at the state level to restrict the substitution of these drugs. This creates an ethical dilemma for pharmacists regarding dispensing of these medications and whether to generically substitute them or not. Anti-substitution laws might go into effect, and might greatly affect the pharmacy profession.

Here is a situation I recently encountered at a community pharmacy where I practice as an intern. I have been interning at the pharmacy for about a year now. A patient came in for a refill on their trileptal medication. While trying to process the refill, I was stopped by the computer because there is a new generic out on the market, oxcarbazepine. Investigating this further, my claim for the refill was rejected because the patient’s insurance company will not approve the brand name anymore. The insurance rejection stated that the patient must take the generic; even though the patient has been stabilized on the brand name. Since I just had my Neurology Module in the pharmacy curriculum, I knew that there are some issues with generic substitution of this class of medications. I tried to discuss this issue and what course of action to take with the pharmacist on duty.

Not surprisingly, the pharmacist was too busy to really discuss the issue with me. The pharmacist stated that the generic is the same exact medication, and didn’t even give it a second thought or consider what my point was. That angered me, not because the
The pharmacist has the professional responsibility to put the patient first, and act with fidelity to provide the best care for the patient. This inspired me to choose this topic and to look more into this issue, because soon I will be making these important decisions when I become the pharmacist.

Since pharmacists are the medication experts, they are fully aware of serious toxicities and adverse events that can occur with generic substitution of narrow therapeutic index medications. Pharmacists face ethical dilemmas in their practice everyday, and generic substitution of narrow therapeutic index drugs is just one of those dilemmas. What is the pharmacists’ duty in this situation? Should the pharmacist generically substitute the product, since it is therapeutically equivalent as approved by the FDA? Or should the pharmacist fight to give the patient the brand name?

A dilemma also arises if the generic substitution becomes legally restricted, and pharmacists must gain approval from the prescriber and the patient before generically substituting certain medications. Pharmacists must act with beneficence, that is, go out of their way to benefit their patients and prevent harm. Preventing harm is a key point here, because as discussed below, there have been reports of toxicity associated with generic substitution of narrow therapeutic index drugs. Pharmacists must also act with fidelity, because it is the pharmacists’ obligation as a healthcare provider to provide the best care for the patient, while staying loyal to the patients.

Pharmacists also face the problem of conflict of interest when dealing with insurance companies and other managed care programs. Most insurance plans do not pay for brand name medications, and force patients to take the generic product, without any
regards to whether that product is considered a narrow therapeutic index or not.

Insurance companies develop formularies so that they can be as economically efficient as possible. However, that is not very ethical because they might be thinking more in terms of finances, and less in terms of the patients’ health.

Generic substitution is fine with most drugs. However, when it comes to narrow therapeutic index drugs, more thought needs to be put in when developing these formularies. Thus, pharmacists are torn between whether they should call the insurance company, fight for the brand, get the prior authorization from the doctor, or just dispense the generic medication. Dealing with honesty with patients, also known as veracity, is key to preserve the covenantal relationship between the pharmacist and the patient.

Pharmacists should discuss with patients the issues with generic substitution of all their medications, most importantly that of narrow therapeutic index drugs. Pharmacist need to make sure that their patients are educated about the possible toxicities associated with generic substitution of these medications, and work with the patient to find the best way to go about the situation.

Most state Boards of Pharmacy allow generic substitution as long as the generic medication is therapeutically equivalent to the brand medication, according to the Orange Book. The FDA publishes its findings regarding therapeutic equivalence in the publication entitled “Approved Drug Products with Therapeutic Equivalence Evaluations”, also referred to as the Orange Book. Currently, the FDA and state Boards of Pharmacy say it is ok to switch A-rated medications, including those with a narrow therapeutic index. Currently, there are actions being taken to limit substitution, especially of antiepileptic medications. For example, the American Academy of
Neurology (AAN) is against the substitution of antiepileptic drugs without the prescriber’s approval and the patient’s consent. The AAN’s argument states that even minor differences between the generic and brand epilepsy medications can cause serious seizures and toxic effects\(^1\).

Despite the statements of the AAN, the FDA and most state Boards of Pharmacy allow generic substitution of these narrow therapeutic index medications. Some states, however, have modified their laws and regulations and added restrictions to this form of generic substitution. The state of South Carolina recommends not substituting some antiepileptics. Likewise, Hawaii requires both patient and prescriber consent before a generic can be substituted for a brand name antiepileptic medication\(^9\). Most data available regarding this issue is concerning antiepileptic drugs. However, concern should be taken regarding other narrow therapeutic index drugs, because minor differences in the generics can cause serious toxicity and adverse effects.

It is important to discuss what a narrow therapeutic index medication is to realize why minor differences in these medications can cause serious toxicity. The therapeutic index of a drug is quantitatively a ratio of the dose of the therapeutic agent that causes the toxic effect to the dose of the therapeutic agent that causes the therapeutic effect. The equation of the therapeutic ratio is:

\[
\text{Therapeutic ratio} = \frac{\text{LD}_{50}}{\text{ED}_{50}}
\]

The LD50 is the lethal dose required to kill 50% of a tested population. The ED50 is the minimum effective dose for 50% of the population. Therefore, a drug with a narrow
therapeutic index means that there is little difference between the therapeutic dose and
the toxic dose. The FDA states that a narrow therapeutic index is defined as: 8
a. There is less than a 2-fold difference in median lethal dose (LD50) and median
effective dose (ED50) values, or
b. There is less than a 2-fold difference in the minimum toxic concentrations and
minimum effective concentrations in the blood, and
c. Safe and effective use of the drug products requires careful titration and patient
monitoring.

In order to be considered a therapeutic equivalent to a brand name drug, a generic
drug product must meet pharmaceutical equivalence and bioequivalence criteria.
According to the FDA, bioequivalence is “the absence of a significant difference in the
rate and extent to which the active ingredient or active moiety in pharmaceutical
equivalents…becomes available at the site of drug action when administered at the same
molar dose under similar conditions in an appropriately designed study.” 6 Drugs are
considered bioequivalent if the 90% confidence interval of the area under the time
absorption curve (AUC) and maximum concentration (Cmax) of the test product is within
80% to 125% of the reference product. 9

Drug products are pharmaceutical equivalents if they contain the same active
ingredient(s), are the same dosage form and route of administration, and are identical in
strength and/or concentration. Also, generic products may contain different excipients
such as colorants, preservatives, lubricants, and diluents which might lead to further
differences between the two products. In most states, pharmacists cannot substitute non-
therapeutic equivalents without the prescriber’s approval. The state Boards of Pharmacy regulate substitution laws, and each have state-specific criteria to be met.

Generic products that are A-rated by the FDA are considered therapeutically equivalent to the brand name product. Drugs given an A rating have no known or suspected bioequivalence problems. AB ratings are for drugs in which actual or potential bioequivalence problems have been resolved with adequate bioequivalence testing. Those products that are not therapeutically equivalent are B-rated. It can be argued that the variability found between brand and generic products of medications is enough to potentially lead to toxicity and adverse events.

Some examples of narrow therapeutic index medications include:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
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<tbody>
<tr>
<td>Phenytoin</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Valproate</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Cardiac Glycoside</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Thyroid Hormone</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Methylxanthine</td>
</tr>
<tr>
<td>Lithium Carbonate</td>
<td>Mood Stabilizer</td>
</tr>
<tr>
<td>Vancomycin, Gentamicin</td>
<td>Aminoglycoside Antibiotics</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Antipsychotic</td>
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</table>

(A few of the medications listed in the table will be discussed to see why generic substitution of narrow therapeutic index medications is an important ethical issue)

Cases and studies have been reported of toxicity occurring with generically substituted medications. Phenytoin is the most studied antiepileptic medication when it comes to comparing brand and generic forms. Reports of toxicity with generic substitution of phenytoin were first reported in the 1960s. Most of these case reports
occurred due to a change in the excipients, and most occurred in Australia. Numerous studies have been conducted since then, and have shown results of significant differences in serum concentrations of phenytoin between the generic and brand products, as well as among different generic products. Bioavailability is particularly an issue if a drug has low water solubility, a narrow therapeutic index, and/or nonlinear pharmacokinetics.

For example:

<table>
<thead>
<tr>
<th>AED</th>
<th>Low Water Solubility</th>
<th>Narrow Therapeutic Range</th>
<th>Nonlinear Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Valproate</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The VA conducted a retrospective chart review study in August 1987. It showed that patients who were given generic phenytoin had a 22% to 31% lower serum concentrations than patients who were given dilantin (brand name of phenytoin). Due to the study results, a recall of the generic phenytoin was conducted by Sidmak Laboratories in December 1987 after some batches failed dissolution specifications.

Another study was conducted in 1992 (n = 12). This was a single blind, crossover study consisting of seven 4-week treatment periods. Patients were given epanutin capsules (brand name for phenytoin), epanutin infatabs, and three other generic phenytoin tablets. Serum concentrations from blood samples were taken after a 12-hour period. There were differences noted in the bioavailability of the products. The generic product difference in bioavailability to the brand name epanutin capsules ranged from 76% to 121%. There was no difference in seizure control or adverse effects among the different phenytoin formulations. However, the authors of the study did conclude that substitution
of one generic phenytoin for another can potentially lead to problems with seizure control and adverse effects.\textsuperscript{5}

Phenytoin is considered a narrow therapeutic index drug primarily due to its Michaelis-Menten pharmacokinetics. The nonlinear nature of phenytoin’s metabolism leads to a very steep dose-response curve. As the patient nears the steep portion of the dose-concentration curve, a very small increase in the dose will lead to a disproportionate increase in plasma concentration, and often, toxicity. Phenytoin is also highly protein bound to both serum albumin and alpha-1-acid glycoprotein. Fluctuations in unbound phenytoin can occur in many disease states (e.g., congestive heart failure, closed head injury, critical illness, malnutrition).\textsuperscript{4}

A number of studies have shown variations in the pharmacokinetic characteristics that caused breakthrough seizures due to generic substitution of carbamazepine. Over 20\% of cases of loss of efficacy are traced to lowering of serum levels following a switch to a generic product. Thus, it has been reported that replacement of brand name tegretol with generic carbamazepine results in a higher incidence of neurological side effects and skin rash. Here is a compiled list of some of the case reports following replacement of tegretol with carbamazepine:\textsuperscript{12}

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report of a 16 year old boy</td>
<td>Boy with partial epilepsy caused by cerebral hemiatrophy stable on Tegretol experienced convulsions when switched to the generic</td>
</tr>
<tr>
<td>Case report of 3 patients</td>
<td>Loss of seizure control following generic substitution of Tegretol, with restoration of control when Tegretol reinstated</td>
</tr>
<tr>
<td>Case report of a woman</td>
<td>Seizure activity increased following generic substitution of Tegretol, with fall in serum carbamazepine level. Control regained when Tegretol reinstated</td>
</tr>
</tbody>
</table>
Case report of 2 patients  Breakthrough seizures occurred within 3–7 days of generic substitution of Tegretol

Case reports of 2 patients  Breakthrough seizures associated with drop in serum levels of carbamazepine following switch from Tegretol to generic

Case reports of 2 6-year-old children  Increases in carbamazepine $C_{\text{max}}$ of 22% and 41% after mandatory generic substitution, resulting in toxicity that reversed when Tegretol reinstituted. One child required hospitalization

Dupont Merck has been opposing unlimited generic substitution of narrow therapeutic index drugs since 1996 in at least 23 states. The company’s efforts are to require pharmacists to obtain physician approval before switching a patient to a generic, particularly concerning the generic substitution of their brand name coumadin to the generic warfarin. It has been suggested that this is actually Dupont Merck’s effort to maintain their monopoly on the drug coumadin. In 1996, Dupont Merck sent a petition to the FDA and the USP requesting the agencies to change the bioequivalence standards of the generic product. The petition was rejected by the FDA in March 1997 with the FDA stating that "...there is no documented scientific evidence of safety or efficacy problems with these drugs. In the absence of such evidence, it is not necessary at this time to require studies that are more stringent than those that have been accepted in the past to establish bioequivalence in drugs with narrow therapeutic ranges." The USP also rejected the petition, stating that "panel members are not aware of any clinical problems that have arisen from current requirements".\(^{11}\)

In contrast, Barr Laboratories released an observer-blind, randomized, crossover study using the two forms of warfarin sodium, brand and generic. The study involved 39 patients with atrial defibrillation who were kept on constant doses of the two
formulations. The results showed the two drugs were bioequivalent within the specified norms and demonstrated no differences in side effects.\(^3\)

The table below shows that the variability around the mean INR before enrollment for those patients who then took the generic product were not significantly different from the variability around those patients' mean INR after enrollment. The before-and-after INR differences in the conversion group (0.15) and control group (0.18) were small, not significant, and of negligible clinical meaning. Use of the generic warfarin sodium product (Barr Laboratories) in patients previously receiving the brand name product (Dupont Merck) did not change the INRs more than did continued use of the innovator product by another group of patients.\(^3\)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>All Patients</th>
<th>Mean ± S.D. INR</th>
<th>Dosage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conversion Group (n = 105)</td>
<td>Control Group (n = 105)</td>
<td>Conversion Group (n = 74)</td>
</tr>
<tr>
<td>Before enrollment</td>
<td>2.6 ± 0.4</td>
<td>2.6 ± 0.4</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>After enrollment</td>
<td>2.7 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>2.6 ± 0.4</td>
</tr>
</tbody>
</table>

(International Normalized Ratios (INRs) in Patients Who Switched or Did Not Switch to Generic Warfarin Sodium)\(^3\)

Roger L. Williams, M.D., a director for the pharmaceutical science center of the Center for Drug Evaluation and Research, backed up the FDA’s position regarding narrow therapeutic index drugs and that they "can be substituted with the full expectation by the patient and physician that they will have the same clinical effect and safety profile as the innovator drug". Dupont Merck had captured the market sales for the medication coumadin, and the company was fighting to extend the patent. The manufacturer tried to keep the generic off the market by attempting to change the FDA standards, but it was unsuccessful.\(^{11}\)
Antiarrhythmic medications are also considered narrow therapeutic index agents. In 1997, The American Heart Association distributed a survey to assess the attitudes, beliefs, knowledge, and experience of physicians on generic drugs and generic substitution. More importantly, it assessed their perceptions of the therapeutic index for 15 branded drugs and comfort in substituting those products with generic alternatives. The survey was sent to 3,369 physicians nationwide. Cluster analysis was the method used to analyze the results. Surprisingly, only 17% of physicians could correctly identify the FDA standards for bioequivalency.²

It is important to look at the pharmacists’ view and position on this issue, since they are the healthcare provider who is dispensing and counseling patients on their medications. Banahan et al. uncovered pharmacists' concerns regarding generic substitution with certain narrow therapeutic index drugs. Pharmacists in these samples clearly believed generic substitution should not be allowed for certain drugs, even though therapeutic failures of generic medications were not generally seen as a serious problem. This occasionally places pharmacists at odds with some insurances and managed care programs. Some of the results of the survey are displayed in the table below:¹⁰

<table>
<thead>
<tr>
<th>Statement</th>
<th>Community Pharmacists (n = 830)</th>
<th>Hospital Pharmacists (n = 460)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic failures are a serious problem with some generic products.</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Dosing on some prescription drugs is too critical to accept the wide range of variability that FDA allows among generic drugs.</td>
<td>4.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Being required to dispense</td>
<td>4.6</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Several studies in the 1990s examined pharmacists' views on suitable versus non-suitable candidates for substitution. The products that were on top of the pharmacists' lists of poor candidates for substitution were: warfarin (coumadin), phenytoin (dilantin), and digoxin (lanoxin). Pharmacists were also particularly hesitant to substitute generics for carbamazepine (tegretol), levothyroxine (synthroid), and procainamide (procanbid SR).

I conducted a survey to assess pharmacy students’ opinions on the issue of generic substitution of narrow therapeutic index drugs. The survey was sent electronically to pharmacy students in their 2nd and 3rd professional years at Wayne State University Applebaum College of Pharmacy. A total of 91 students took the survey. Of these 91 students, 11% said these drugs are very dangerous and should not be substituted, 42.9% reported that the substitution is dangerous, 24.2% said it was safe, and 22% were not sure. In another question, I created a scenario for the students to pretend that they were the patient, and are stabilized on the antiseizure medication tegretol for 3 years, and now a generic came out. If the student was the patient, would they request the brand or switch to the generic medication? The responses were: 63.7% would request the brand, 20.9% would take the generic, and 15.4% have no preference.
These responses are interesting when looking at another question in the survey: “Have you ever considered this issue (generic substitution of narrow therapeutic index drugs) or given a second thought before switching a patient from a brand to a generic?” Only 28.9% selected “Always” to this question. Yet, as seen in the previous question, 63.7% of those surveyed requested the brand for themselves if they were the patient. It is important for these students to realize that when such issues arise, they need to put themselves in the patient’s shoes and look at all the things that can happen. It is the pharmacist’s obligation as a healthcare provider to provide the best care for patients, and to act with honesty and loyalty. I think that when pharmacists are dealing with patients, they really need to think of what they would do for themselves if they were the patient. The ethical principle of beneficence, the pharmacist’s obligation to benefit the patient, prevent harm, and go out of his/her way to help the patient really comes into play here.

Here are some of the surveyed students’ responses to a short answer question on generic substitution of narrow therapeutic index drugs:

“Never switch between seizures drugs even brand names (come on...everyone knows that.....)no...NTI..not safe”

“Definitely understand how patients may feel about this issue because if I was in their position, then I'd think twice about changing the medication. So basically, I wouldn't want to change it if it was like something that could affect my life like Warfarin or AEDs. But if it was synthroid, I think I will be ok with it because there are lab tests that can be done and I would know if the generic allowed me to be therapeutic or not. Then again this is coming from a healthcare perspective. The average patient will not know this information”.

“If it were me (or a loved one) I would not take any chances”

“I would switch to the generic. The generic version can be titrated just as easily as the brand. May just need to re-check blood levels. But I would not recommend switching around on a regular basis. Switch and make sure pt is stable and then leave it alone”
Going back to a question discussed above, most students in the survey chose to stay on the brand name medication if they were the patient. Choosing to stay on the brand is much easier said than done. It is important to take into account the consequences of requesting the brand name. Some of which are the cost, the high probability that their insurance will not pay for it, and the likelihood that their doctor will not do a prior authorization to attempt to get their insurance company to change it. There is also the hassle of going back and forth between the pharmacy and doctor’s office, and the fact that all these are time-consuming processes.

I also assessed the students’ opinions on whether the generic substitution of these narrow therapeutic index drugs should be restricted or not. That is, if a patient was on a brand name medication, the pharmacist cannot switch the patient to a generic before obtaining physician and patient consent. Of the respondents, 60.9% said they would favor the regulation and that it will promote safety, while 14.9% opposed it, believing that it would hinder the pharmacists’ expertise and clinical judgment. And 24.2% were not sure about this issue. I also asked the students if they felt like they needed more education on this topic. The majority of the students, 79.1%, said yes they needed more education, while 20.9% said no, they did not need any more education on this topic.

An important component of pharmacists' views on generic products is the pressure they feel to increase and promote the use of generic medications from managed care and other insurance plans. This pressure is unethical, creating a conflict of interest, and the pharmacist might be pushed to do things that might not be in the best interest of the patient. Banahan and colleagues assessed community pharmacists’ responses to a question on whether managed care plans had forced them to dispense a generic product
when in their professional opinion substitution was not in the best interest of the patient. The results showed that pharmacists are indeed under pressure from third parties to substitute generic products. Analysis showed that 60% of community pharmacists surveyed had encountered that situation, and virtually all (98%) thought it would arise more frequently in the future.¹⁰

Like community pharmacists, 93% of hospital pharmacists believe that they will face greater pressure to use an inappropriate generic product in the future.¹⁰ This becomes an ethical dilemma for pharmacists, because even though they might think that staying on the brand name of the medication is better for the patient, they are hindered by the insurance companies. The pharmacist must deal with justice and fidelity with patients, and preserve the special covenantal relationship with them. Therefore, pharmacist should not allow insurance companies to pressure them to do things that they believe might not be in the best interest of the patient. From my internship experiences, I have faced the same pressures and dilemmas. Most third party plans do not cover a brand product if a generic is available. That forces me to switch the patient to the generic because most patients cannot afford the prices of the brand name products, even though I might not agree with that switch.

Besides the insurance and third party issues, pharmacists also face pressure on generic substitution from their patients. Banahan and colleagues assessed the pharmacists’ beliefs on their patients’ view of generic products. The results to the statement "Patients want me to dispense generics," the average response for community pharmacists was 5.2 (Based on a scale where 1 = strongly disagree and 7 = strongly agree.). Pharmacists strongly expressed that patients wanted generic products. In
addition, pharmacists reported that 72% of patients accepted generic medications when the pharmacist recommended them. The main reason for patient’s strong acceptance of generic products is that they are more economically efficient. The pharmacists surveyed believed that patients' demand for lower cost generics may not be great enough to justify third party plans' insistence on their use. Other important factors pharmacists use in selecting a product are quality, supplier consistency, and manufacturer reputation.

It is clear that generic substitution of narrow therapeutic index medications poses ethical dilemmas for pharmacists. For example, if a patient has been stabilized on a narrow therapeutic index medication and a generic product came out on the market, what should the pharmacist do? Knowing that the generic product might lead to inefficacy or toxicity, the pharmacist might be reluctant about switching the patient to the generic formulation. However, this is hindered by third parties who will refuse to pay for the brand, physicians who will refuse to do prior authorizations, as well the cost of the brand name medication.

A good way to look at this situation is if the pharmacist places him or herself in the patient's shoes. What if the pharmacist was stabilized on an antiepileptic medication and a new generic came on the market. Would the pharmacist switch themselves to the generic, or would they request the brand? The pharmacist should analyze the situation and look at all the advantages and disadvantages of switching to the generic form. If the pharmacist requests the brand for themselves, will he/she do the same for their patients? Are they willing to take the time to deal with third parties, physician prior authorizations, economic inefficiency, all while they are busy filling other prescriptions? Will the
pharmacist be held liable if the patient’s condition worsens due to the generic substitution? These are all questions that pharmacists go through when faced with such a dilemma.

Opponents of the restriction of generic substitution argue that pharmacists are in the best position to evaluate the appropriateness of generic drug substitution. Pharmacists should have the right to use their clinical judgment, knowledge, and professionalism in generic substitution. Therefore, when pharmacists are substituting a generic product for a patient who has been stabilized on a brand name, they should stop and think a little before automatically substituting. The pharmacist should look at the risk v. benefits ratio, and notify all parties involved about the substitution (i.e. prescriber, patient, caregiver, parent/guardian). The pharmacist should counsel the patient on the issues surrounding the substitution, and encourage the patient and the prescriber to closely monitor the patient and the condition.

For example, if the substitution is with an antiepileptic agent, the patient’s serum levels of the medication should be closely monitored to avoid inefficacy or toxicity. If the substitution occurred from coumadin to warfarin, the patient’s INR should be closely monitored. Likewise, if the substitution occurred between synthroid and levothyroxine, thyroid blood levels should be monitored, and so on. The pharmacist should also educate the patient to be on the lookout for signs and symptoms of their condition. The pharmacist should always act with veracity with patients, the foundation upon which stands the relationship between the pharmacist and the patient. The main point is that the patient should know that they are being switched to a generic and therefore must be closely monitored.
Professional organizations’ stands on this dilemma can help pharmacists frame their thinking and actions regarding generic substitution, especially when it comes to narrow therapeutic index drugs. For example, the American Pharmacist’s Association (APhA) plays a critical role in the support of the repeal of anti-substitution laws. APhA supports the pharmacist’s role in identifying generic products as a means of reducing costs. The American Society of Health-System Pharmacists advocates a strong role for pharmacists in proposing opportunities for generic substitution, including evaluating the data available to make determinations of therapeutic equivalence. Likewise, the National Community Pharmacist’s Association states that “Pharmacists should be involved in the drug decision process to encourage cost savings while preserving therapeutic standards of drug therapy”.¹⁰

Between the years 1997 and 1998, at least 32 states had some sort of legislation introduced or other activity by lobbyists from brand name manufacturers to restrict access to generic narrow therapeutic index drugs. To date, however, such legislation has passed in only a few states: Texas, Virginia, Hawaii, North Carolina, and South Carolina. The legislation is a supplementation to the state’s own product selection laws. The legislation defines a narrow therapeutic index drug and lists specific drugs that are considered to be in that category. The legislation prohibits pharmacists from refilling a prescription for a narrow therapeutic index drug with one made by a different manufacturer unless the pharmacist obtains documented consent from both the patient and the prescriber⁴.

Of course there are always at least two sides to a story. Therefore, pharmacists have mixed views regarding this legislation. Some pharmacists think this legislation will help patients and promote their safety, while other pharmacists believe that this threatens
the pharmacy profession, and pharmacists are knowledgeable enough in the field and their scope of substitution should not be restricted.

A big concern pharmacists have is liability. Some of the literature on this topic suggests that a pharmacist’s potential liability in the drug product selection process is greater when a narrow therapeutic index drug is substituted than when other types of drugs are substituted. The Federal Trade Commission’s Model Drug Product Selection Act contained a provision designed to limit a pharmacist’s civil liability when substituting a generically equivalent drug in place of the brand name product. It states: “Any pharmacist who selects an equivalent drug pursuant to this section incurs no greater liability in filling the prescription by dispensing the equivalent drug product than would be incurred in filling the prescription by dispensing the brand name drug prescribed”⁴. States today have the same type of provision in their product selection laws. The effect of it is that if pharmacists comply with their state’s product selection laws, they may incur no greater liability than if they had dispensed the name brand drug product. It is important to note that these provisions do not differentiate between narrow therapeutic index drugs and other drugs.⁴

Some of the literature on this topic suggests that a pharmacist’s potential liability in the drug product selection process is greater when a narrow therapeutic index drug is substituted than when other types of drugs are substituted. It is often cited that narrow therapeutic index drugs are involved in many claims against pharmacists. It is essential to realize that these drugs are more likely to be involved in liability suits, whether they are generically substituted or not.⁴
In summary, generic substitution of medications has become a widespread practice since the FDA approves bioequivalent drugs, and generic substitution aids in trimming healthcare costs. Theoretically, it is ok to substitute a brand name drug with its generic counterpart if it is bioequivalent to the brand name. For most drugs, generic substitution is safe and effective, and the FDA has supported it with studies and research. Even if a physician prescribed a brand name medication, the pharmacist may dispense a generic unless the physician specifically states on the prescription that the brand cannot be substituted for. If a generic substitution does occur, especially with narrow therapeutic index drugs, it is critical to inform all parties affected (i.e. patient, prescriber, caregiver, parent/guardian).

In some cases, generic substitution may not be appropriate. Although the brand and generic forms of a medication have the exact same active ingredients, other excipients such as diluents, coatings, and fillers used in the formulations affect how the drug is absorbed and released in the bloodstream. For these medications, slight changes in dosage could result in blood level fluctuations leading to either ineffectiveness or toxicity. The issue of generic substitution restriction of narrow therapeutic index drugs will always be present if drug manufacturers continue to exist and compete.

Pharmacists face ethical dilemmas in their daily practice, and generic substitution of narrow therapeutic index drugs is just one of these dilemmas. When it comes to ethical issues, the laws and regulations do not provide a right or wrong answer to pharmacists. Therefore, pharmacists need to utilize tools provided by the profession, combined with their own personal values, to guide them in the decision making process in these kinds of situations. Pharmacists have a professional responsibility to provide the
best care for their patients. Guided by their own morals, ethical principles, and the code of ethics, pharmacists can make their decisions. Each pharmacist has their own personal code of ethics that they follow in their daily practice. For example, in my daily living, I try to treat others the way I want to be treated. I can incorporate this ideology into my professional practice by delivering the same quality of service and care to my patients as the quality of care I expect to receive when I am the patient. That means I will do my best, and go above and beyond in certain cases, to make sure the patient receives the maximum benefit of care that I would want to receive.

Placing restrictions on generic substitution of narrow therapeutic index drugs remains a controversial issue. Pharmacists must follow their ethical duties and obligations to provide the optimal care for patients. A simple test that can be done is the pillow test, performed when pharmacists go to sleep at the end of the day. Whatever the pharmacists’ decision regarding the ethical dilemma was, what’s important is that: Their actions were out of good intentions for the patients, they acted with fidelity and honesty, followed their professional obligations, and maintained the covenantal relationship with the patient. They can then rest assured, knowing that they provided the best care within their power for their patients.

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