# Illegal "No Prescription" Internet Access to Narrow Therapeutic Index Drugs

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## ABSTRACT

**Background:** Narrow therapeutic index (NTI) drugs, because of proximity of therapeutic amounts to toxic amounts, require close professional oversight, particularly when switching formulations. However, safe use may be compromised by unsupervised switching through access to online "no prescription" Web sites.

**Objective:** We assessed no prescription online availability of NTI drugs, using an academically published list (core NTI drugs).

**Methods:** Using the Google search term "buy DRUG no prescription," we reviewed the first 5 search result pages for marketing of no prescription NTI drugs. We further assessed if National Association of Boards of Pharmacy (NABP) Not Recommended vendors were marketing NTI drugs. Searches were conducted from November 3, 2012 to January 3, 2013.

**Results:** For core NTI drugs, we found 13 of 14 NTI drugs (92%) marketed as available without prescription, all from NABP Not Recommended vendors. On the basis of these initial findings, we expanded our core list to 12 additional NTI drugs; 11 of 12 of these drugs (92%) were available from no prescription Web sites. Overall, 24 of 26 NTI drugs (92%) were illegally marketed as available online without the need for a prescription.

**Conclusion:** Suspect online NTI drug access from no prescription vendors represents a significant patient safety risk because of potential patient drug switching and risk of counterfeit versions. Further, state health care exchanges with coverage limitations may drive patients to seek formulations online. Food and Drug Administration harmonization with tighter international NTI drug standards should be considered, and aggressive action against suspect online marketers should be a regulatory and public health priority. (*Clin Ther*. 2013;35:694–700) 

**Key words:** Internet, narrow therapeutic index drug access, no prescription, online pharmacies.

## INTRODUCTION

Narrow therapeutic index (NTI) drugs are those that show small differences between therapeutic and toxic amounts and therapeutic and ineffective amounts.[1] Hence, the dosing range required to achieve the desired effect with NTI drugs is narrow, with sub-range doses resulting in dangerous therapeutic failures and supra-range doses resulting in toxic adverse effects. These pharmacodynamic responses with the potential for adverse patient safety events are especially relevant in vulnerable groups such as older patients, patients with comorbidities, or patients taking multiple medications.[2] Indeed, patients taking NTI drugs have double the associated adverse event incidence than patients taking non-NTI drugs (40% vs 19%, respectively).[1]

As a consequence of the narrow range for safe use of these drugs, monitoring patients closely during initiation and use of an NTI drug is imperative. The "start low and go slow" mantra is often repeated among cli-

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nicians with the start of medications such as phenytoin, tacrolimus, or digoxin—all NTI drugs.[3,4] Further, a number of studies have shown that monitoring of NTI drug levels for a variety of therapeutic classes can ensure appropriate therapeutic dosing and can promote patient safety outcomes.[3,5–9]

In addition, the narrowed range of NTI drug therapeutic safety warrants vigilant clinical monitoring when switching formulations.[2,3,5] The dangers associated with brand-to-generic, brand-to-brand, or generic-to-generic switching arise from variable active ingredient bioavailability.[2] As an example, NTI antiepileptic generic bioequivalents have been reported as having a lower degree of activity in patients than the same dose of the brand form and can result in otherwise stable patients having seizures during transfer between formulations.[6]

However, even in the highly controlled US drug regulatory environment, with generics that are approved by the US Food and Drug Administration (FDA) as bioequivalent to the corresponding brand drug, the risk of insufficient bioequivalence that results in adverse NTI drug events has warranted regulatory guidance.[10] The Department of Health and Human Services, for example, recommends limiting a pharmacist's discretion in NTI generic drug substitution.[11] Further, some states prohibit NTI generic drug substitution without the prescriber's explicit consent.[11] Although this risk exists, the FDA does not have an official list of NTI drugs for appropriate clinician and patient identification, whereas other countries have identified and targeted these compounds.[12]

In addition, propelled by cost-containment provisions in the recent US Affordable Care Act, campaigning has been widespread to substitute brand drugs with generics as soon as they become available. In fact, under the Act, state-based insurance exchange drug coverage will likely include limitations to restrict access to 1 or 2 drug formulations.[13]

Limiting patient access to preferred drug formulations may result in an alternative pathway of questionable access: the Internet. Despite global regulatory warnings that detail the unique dangers of purchasing pharmaceuticals online,[14,15] patients increasingly turn to online pharmacies to avoid coverage-based limitations and/or to reduce their overall out-of-pocket pharmaceutical costs. In fact, a recent FDA survey found that close to one-fourth of surveyed patients admitted to buying drugs online.[16] However, online drug consumption is not limited merely to lifestyle drugs. Indeed, studies have identified online illicit marketing and sale of pharmaceuticals that include a number of therapeutic categories, including vaccines, FDA shortage drugs, contraception treatments, and essential lifesaving drugs.[14,15,17–20]

These illegal online pharmacies have been found to be marketing and selling counterfeit, substandard, tainted, or otherwise adulterated product.[14,15] Online drugs are often marketed and sold as "no prescription required" and lack necessary risk-related information on their Web sites to warn patient-consumers of possible side effects, contraindications, and other potential for adverse safety events,[14,15] issues particularly pertinent to patients who use NTI drugs. These questionable online vendors also deceptively market products as "generics" (even when no generic formulation exists) at extremely low pricing and target patients with limited access to health insurance or patients with low online health literacy.[15,21,22] As a result, patients may have a financial interest in switching to lower cost online alternatives, including NTI drugs. However, we were unable to identify data or studies on whether these high-risk drugs are being sold by suspect, no prescription online pharmacies.

To assess this potential patient safety concern, we examined whether NTI drugs are available online without a prescription, a clear indication of a suspect vendor and a clear patient safety risk. We also determined whether identified Web sites were classified by the National Association of Boards of Pharmacy (NABP) as Not Recommended, a further risk indicator for online sourcing of drugs.

## METHODS

Because the FDA has not established an official list of NTI drugs, we used an initial group of 13 NTI drugs identified from the academic literature (aminoglycosides [ie, amikacin and gentamicin], cyclosporine, cabamazepine, digoxin, digitoxin, flecanide, lithium, phenytoin, phenobarbital, rifampicin, theophylline, warfarin).[1] We also included Wellbutrin XL 300 mg, whose Teva generic formulation had its FDA approval withdrawn because of side effects and lack of therapeutic equivalence to the originator product, which expanded the initial study NTI drug list to 14.[23] This was defined as our core NTI drug list. We used the popular Internet search engine, Google, using the search term