

Side Effects: Predictable, Understandable and Avoidable?

While medications have revolutionized our ability to treat illnesses, they are nevertheless responsible for a substantial amount of suffering as well. Side effects due to drugs are the leading cause of hospitalizations. Annually in the USA 2.2 million people are hospitalized and 100,000 people die from drug side effects.⁽¹⁾ These totals do not include side effects due to errors in administration, non-compliance, intentional over dosage, drug abuse or therapeutic failures. Seventy six percent of side effects that led to hospitalization were due to too much drug. What is it about our system of drug development and delivery that results in 76% of side effects being caused by too much drug?⁽¹⁾

Your Genes: Uniquely Yours

A drug's impact - good or bad - is largely determined by the genetic make up of the individual. This takes two forms a) the genetically determined detoxification machinery of the body and b) the genetically determined biological target for the medication.

Most drugs are detoxified to an inactive state before they are eliminated from the body. These detoxification enzymes are under genetic control. If the genes are defective then the drugs cannot be detoxified. This results in the accumulation of excessive amounts of drug and the resulting side effects.

A drug's impact on the body is brought about by blocking a specific enzyme or specific receptor (the biological target). These enzymes and receptors are also under genetic control. Through inherited genetic variation a receptor or enzyme may escape a drug's effect. This means that the drug simply won't work in an individual with this genetic variation and another drug or drug class needs to be selected. Because these types of genetic variations result in a lack of medication efficacy rather than side effects (which is the focus of this article) they will not be discussed further here.

The Detoxification Of Drugs

The most important detoxification machinery in the body is the Cytochrome P450 system of the liver. Cytochrome P450 is a family of enzymes that detoxify most drugs and foreign chemical substances ingested by the mammalian body. Inherited genetic variations mean that some individuals are incapable of detoxifying (or metabolizing) certain substances while other individuals with a different variation in the same gene may be ultra fast metabolizers. In one situation, a standard dose may cause serious side effects because the person's genetically determined enzymes are not able to detoxify a drug. In another person, the drug may be metabolized so fast that blood levels of the drug never get high enough to exert the desired beneficial effect. Below are some examples of the genetic variations in drug detoxifying enzymes.

One member of the Cytochrome P450 family of detoxifying enzymes is called CYP2D6. See the table below for a list of drugs metabolized by this enzyme.

Table 1

CYP2D6				
Drug Class	Beta Blockers	Antidepressants	Antipsychotics	Others
Drug substances	Carvedilol Metoprolol Propafenone Timolo	Amitriptyline Clomipramine Desipramine Doxepin Imipramine Paroxetine Venlafaxine	Haloperidol Risperidone Thioridazine	Atomoxetine Codeine Dextromethorphan Flecainide Mexiletine Ondasetron Propanfenone Tamoxifen Tramadol

Seven percent of Caucasians have an inactive CYP2D6 enzyme and 50% of Asians have reduced enzymatic activity. Based on this genetic information it is possible to predict that about 1 in every 14 Caucasians given standard strengths is at risk of serious side effects because of dangerously high blood levels of the drug. One in two Asians have a high probability of experiencing side effects when taking any of the above listed drug substances.

In contrast 29% of Ethiopians and 10% of Southern Europeans have inherited CYP2D6 genes with duplications. These duplications result in ultrarapid metabolism of the above listed drug substances. The implication of this observation is that one in three Ethiopians on standard strengths will not attain blood levels capable of achieving the desired therapeutic effect.

Another member of the Cytochrome P450 family of detoxifying enzymes is called CYP2C19. See the table below for a list of drugs metabolized by this enzyme.

Table 2

CYP2C19				
Drug Class	Proton Pump Inhibitors	Antidepressants	Anti-epileptics	Others
Drug substances	Omeprazole Lansoprazole Pantoprazole	Amitriptyline Clomipramine	Diazepam Phenytoin Phenobarbitone	Cyclophosphamide Progesterone

Alterations in the gene responsible for the CYP2C19 enzyme result in an enzyme that is incapable of metabolizing the drug substances in table 2.

Up to 25 percent of Asians may have a copy of this altered gene and thus are not able to adequately detoxify the drugs listed in table 2. In contrast, less than 5 percent of Caucasians have this altered gene.

The above two examples represent two of the six Cytochrome P450 enzymes known to detoxify drugs. Genetic control of many detoxification pathways has not yet been fully explored. Other factors also influence drug detoxification. Some of these factors include the amount of drug consumed relative to body size, other medications taken at the same time that may inhibit or compete for detoxification enzymes, and age associated decrease in function of the organs of detoxification such as liver and kidneys. Even with these other contributory factors inherited variations in detoxification enzymes are likely the most important factor because it is fixed throughout an individual's life.

Understanding The Origins Of Excessive Drug Dosing

The Drug Manufacturing Process

The drug manufacturing process has its roots in the nineteenth century industrial model. Drugs are manufactured in one or two centralized locations from which a company supplies the world. Typically a manufacturer will produce two or three strengths of a given product, sometimes more for a high sales volume product.

For purposes of illustrating the point it is useful to examine a frequently prescribed drug. Venlafaxine was picked for no other reason than that it is widely used in both family and psychiatric practices. The information is taken from the Effexor® (brand of venlafaxine) monograph found in the Compendium of Pharmaceuticals and Specialties 2005.⁽²⁾

Table 3 Efficacy of venlafaxine in the treatment of Generalized Anxiety Disorder (GAD)
Percent of patients much improved

Study #	Placebo	37.5 mg	75.0 mg	150 mg	225 mg
1. (210 US)	49 %	-	57 %	58 %	65 %
2. (214 US)	39 %	-	62 %	49 %	
3. (378 EU)	45%	59%	69%	78%	

Based on three 8-week studies in a population of patients, venlafaxine is statistically better than placebo for the treatment of generalized anxiety disorder. It is on the basis of these studies that the drug was “approved” in Canada for the treatment of generalized anxiety disorder. In table 3 four strengths are listed. Each of the first three strengths is 100% stronger than the next highest strength. The fourth, a 225-milligram strength, is 50% higher than the 150-milligram strength. These standardized factory sourced products are expected to work for everyone. That is like a shoe manufacturer making only two or three shoe sizes for the entire world. It will work but is prone to side effects like tripping and falling and cramped, painful toes. There is nothing about human biology that requires a doubling of the strength to 75-milligrams if a 37.5-milligram strength does not work. Nor is there an absolute requirement for 150 milligrams if the 75-milligram strength doesn't work.

The 0.5 milligram part of the 37.5-milligram venlafaxine strength clearly demonstrates that the available strength is an artefact of the manufacturing process and not of human need. If the next closest available strengths to 37.5 milligrams was 37 or 38 milligrams a 0.5 milligram increment would probably have therapeutic rational. But, when the next available strength is 75 milligrams there is only one conclusion to be drawn, 37.5 milligrams happens to be one half of 75.

In the clinical trial results summarized in table 3, the 37.5-milligram strength seems to work as well in Europeans as 75-milligram strength in Americans. It stands to reason that intermediate doses would also work for some of the patients. The point is that patients should only be subjected to the lowest possible strength they need. Anything higher means the patient is required to detoxify more drug than is necessary, sometimes surprisingly large amounts of excess drug. The amount a person must detoxify is called the bioload.

The concept of bioload raises the question “Why should a patient’s liver be detoxifying 75-milligrams of medication when just possibly 45-milligrams per day may be enough?” On an annual basis such a patient would be taking 66% more medication than required. See calculations in table 4.

Table 4 The Annual Bioload of Different Strengths of Venlafaxine

Medication Strength	Milligrams of product consumed per year (X 365)	Difference in annual consumption between ‘ideal’ strength and available strength
45 milligrams*	16,425	
75 milligrams+	27,375	10,950 milligrams

*Hypothetical ideal patient strength for a given patient.

+Available commercial strength.

In our view it is worth additional effort to find the ideal strength for any given patient in order to avoid the annual exposure of as much as 10,950 milligrams *of excess drug*. The chemical substance represented by this additional and unnecessary amount of drug doesn’t just disappear but becomes an environmental contaminant. Recently, the federal government’s study of pharmaceuticals in drinking water confirmed traces of common painkillers, anti-cholesterol drugs and the antidepressant Prozac® are ending up in the treated water that Canadians drink. ⁽³⁾

Hundred percent strength increments have their origin in manufacturing convenience and are not rooted in human biology. In clinical practice the question should be how can the best possible outcome be achieved with the least possible amount of risk? Many patients give up treatment in frustration because the side effects are intolerable. As explored below the drop out rates reported in manufacturer sponsored clinical trials are artificially low. Manufacturer sponsored clinical trials use very strict patient inclusion and exclusion criteria. The manufacturer wants to enrol a uniform population of patients to rule out confounding illnesses and medications that might reduce the possibility of showing a statistically significant drug benefit and the fewest possible side effects.

The Drug Development Process

The efficacy of a drug is based on clinical studies and the accompanying statistical analysis that demonstrates that in a population of patients the drug product provided a greater benefit than placebo (no treatment). The key here however is population. Efficacy in a population does not automatically translate into efficacy in an individual. What do we know about the population in which it was studied? Is the patient who is about to get the treatment a member of that population? ⁽⁴⁾

Enrolment in drug trials is carried out by means of a protocol with detailed inclusion and exclusion criteria. The manufacturer is interested in studying as uniform a population as possible since this reduces confounding factors of unknown importance. Despite all of the important information in the very lengthy Effexor[®] monograph in the CPS, we do not know the following about the study participants:

1. Patient inclusion criteria
2. Patient exclusion criteria
3. Patient weights (median, average or range)
4. Ethnic origin of study completers
5. Ethnic origin of study dropouts

In table 3 above 37.5-milligrams appears to be as effective in European patients (59%) as 75-milligrams in a population of American patients (57% & 62%). Is that because European patients have a lower body mass index than American patients? When calculated on a milligram per kilogram body weight basis are European patients taking the 37.5-milligram strength getting about the same amount of drug as the American patients taking the 75-milligram strength? Or are there more African-Americans enrolled in the US trials? Is venlafaxine less effective in African-Americans?

The monograph reports that 19% of the venlafaxine and 12% of venlafaxine extended release treated study populations discontinued treatment due to adverse effects. At what dose, calculated on a milligram per kilogram body weight did most side effects occur? Are side effects seen more frequently in certain races or people from certain geographic locations (i.e. due to genetic influences)? Would the patients who discontinued due to side effects have done well on a lower individualized strength? These are all open questions.

Avoiding Side Effects

Genetics is the most important single factor in determining drug side effects. Genetic testing for CYP2D6 and CYP2C19 can provide a useful partial picture but there are so many other genes for which routine testing is not yet available. Another challenge is that diseases, other drugs and environmental factors may further complicate the predictability of drug detoxification.

The most immediate tools available to an individual in predicting drug side effects are a personal and family history.⁽⁵⁾ Where did family members originate? Have parents or siblings experienced side effects or drug “allergies”? Do you have a history of sensitivity to drugs? Have you discontinued a treatment because you just didn’t feel right? These are all hints that you are at higher than normal risk of experiencing a side effect with the next drug you take. If that is the case, it worth discussing with your pharmacist very low starting doses and gradual

increases in strength to get just the right balance of benefit with minimal side effects. Your pharmacist can in turn contact your doctor for the most appropriate prescription regime for you.

Prozac[®] is a trademark of Lilly; Effexor[®] is a trademark of Wyeth.

Literature Cited

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Additional Resources

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Pharmacogenomic Testing

- Roche Diagnostics:
- http://www.roche-diagnostics.com/products_services/amplichip_cyp450.html
- Tm Bioscience: <http://www.tmbioscience.com/productsmain.php>
- Specialty Laboratories: <http://www.specialtylabs.com/spotlight/amplichip.asp>
- PGXL Laboratories: <http://www.pgxl.com/clinician/>
- Genelex Corp: <http://www.healthanddna.com/professional/pharmacogenetics.html>
- Seryx, Signature Genetics: <http://www.signaturegenetics.com/sgtiles/en/corporate/main.jsp?id=1>