Consistency of Pregnancy Labeling Across Different Therapeutic Classes

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Introduction

Thalidomide was seen as a miracle drug in terms of its ability to treat morning sickness and insomnia in pregnant women and became infamous as a result of the teratogenic effects it caused such as phocomelia. As a result of the use of thalidomide during the 1950s and 1960s, the implications of taking certain medications during pregnancy were brought to light (1,2).

In 2009, it was reported that approximately 4.1 million births occurred in the United States alone. It has also been reported that approximately 50% of the pregnancies that occur in the United States are planned. Pregnant women often have to take medication during the term of their pregnancy for chronic conditions such as diabetes, asthma, hypertension, and depression or for pregnancy induced conditions such as nausea. The lack of treatment can be dangerous to not only the mother but to her fetus as well. The most commonly prescribed drugs not including vitamins were analgesics, blood-glucose regulators, and drugs prescribed for anemia. It is estimated that women take an average of 3-5 drugs while they are pregnant. Due to an increasing trend in women having children later on in their lifetime the potential use of medication during pregnancy will most likely increase (4).

The perception of what drugs are considered safe by not only pregnant women but also prescribers is variable and is further complicated by the limited number of clinical studies in pregnant women. Some women hold misperceptions about the associated risks when taking certain medications while pregnant and may end up terminating pregnancies as a result of these perceptions. These misconceptions may also be further exacerbated since many clinicians do not receive specialized training in prescribing medications for pregnant women. In order to make better recommendations and understand potential risks for prescribing medicines during pregnancy physicians often depend on the information provided in a drug's label. In 1979, the A, B, C, D, and X category classification that is based on the adverse events and potential benefits of a particular drug was implemented in the United States in order to standardize pregnancy labeling (As shown in the table below). The current category system has been criticized for being too simplistic because of an implied representation of hierarchy of risk. Therefore pregnant women and clinicians have to depend on the pregnancy labeling to provide them with necessary information to properly use and prescribe medications during the term of the pregnancy (2-6).

FDA Pregnancy Risk Categories	
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women.
	or
	Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women.
	or
	No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.
NA	FDA pregnancy rating not available

Objective

To evaluate the consistency of pregnancy labeling across different therapeutic drug classes for the top 20 therapeutic classes according to the top drugs by pharmaceutical sales in 2010.

Methodology

Top 24 drugs by pharmaceutical sales were taken from Drugs.com listing of the top 200 drugs of 2010. Drugs that were combination products or contained only one drug in their subsequent therapeutic class were not included in this study, leaving 22 drugs.

The Clinical Pharmacology website (http://www.clinicalpharmacology-ip.com/) was used to find the therapeutic categories that the top 22 drugs fell into and the subsequent drugs that shared these classes as well.
The current approved US-FDA labels for these drugs were obtained from the archived label section on Daily Med (dailymed.nlm.nih.gov).

The Pregnancy Section (Section 8.1), and Labor and Delivery (Section 8.2) where available, and the Nursing Section (Section 8.3) were the focus of this study. Drugs that were combination products, off the US market, or had sex specific indications were not included in this study

These labeling sections were then surveyed for the presence of adequate human and animal studies, nonteratogenic and teratogenic adverse events, and pregnancy registry information. Whether or not the drug was reported to cross the placental barrier was also surveyed.

Results

Consistency of Pregnancy Labeling Across Therapeutic Classes

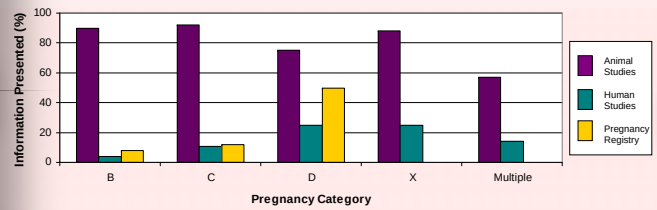
Drug Class	Top Selling Drug (Active Ingredient, Rank)	Same Class Drugs(N)
Proton Pump Inhibitors (PPIs)	Nexium (Esomeprazole,1)	6
Statins	Lipitor (Atorvastatin, 2) and Crestor (Rosuvastatin, 9)	7
ADP Receptor Antagonists	Plavix (Clopidogrel, 3)	4
Opiate Agonists	OxyContin (Oxycodone, 5)	13
Atypical Antipsychotics	Abilify (Aripiprazole,6) , Seroquel (Quentiapine,8), and Zyprexa(Olanzipine,13)	10
Leukotriene Receptor Antagonists	Singulair (Montelukast, 7)	2
ASNRIs	Cymbalta (Duloxetine,10) and Effexor XR(Venlafaxine,19)	3
Thiazolidinediones	Actos (Pioglitazone,11)	2
SSRIs	Lexapro (Escitalopram,12)	6
Antimanic Agents	Zyprexa (Olanzapine,13)	5
Respiratory Antimuscarnics	Spiriva (Tiotropium,14)	2
Insulins	Lantus (Insulin Glargine,15)	6
Cholinesterase Inhibitors	Aricept (Donepezil,16)	3
Analgesics/ Analgesic/Misc. and Neurological Agents	Lyrica (Pregabalin,17)	6 and 9
Angiotensin II Receptor Antagonists	Diovan (Valsartan,18)	8
Adrenergic Agonists and ADHD, Non-Amphetamine	Concerta (Methylphenidate, 20)	2 and 12
Quinolones	Levaquin (Levofloxacin, 21)	6
Dipeptidyl Peptidase-4 Inhibitors	Januvia (Sitagliptin,24)	3

* Advair Diskus (4) and Diovan HCT(23) were not included in this listing since they are combination productions
Celebrex(22) was also not included since only one drug fell into the COX-2 Inhibitors therapeutic class

Out of the 20 therapeutic classes surveyed in this study, nine were consistently labeled with a pregnancy category across class.

Consistency of Labeling Information Within Pregnancy Categories

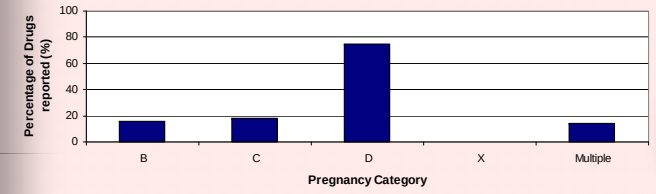
Presentation of Human and Animal Studies and Pregnancy Registry Information



*Human Studies were defined as post/pre market, epidemiological studies, or independent studies reported in the label. Human Adverse Event reports were not limited to studies but also included reports that were mentioned in the label. None of the drugs were classified as pregnancy category A.

Seven of the eight drugs in the Angiotensin II Receptor Antagonists therapeutic class fell into more than one pregnancy category (C/ D) depending on the trimester

Percentage of drugs reported that cross the placental barrier

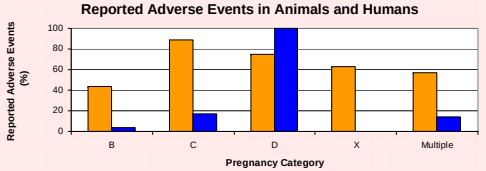


*Many of the drugs that reported the transfer of drugs across the placental barrier did not distinguish between animal and human transfer. There are no data available for the category X drug

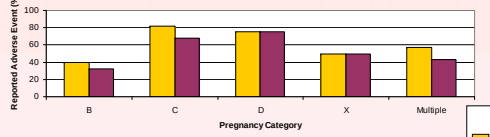
Results (Cont'd)

Presentation of Adverse Events Drugs in the Top 20 Therapeutic Categories

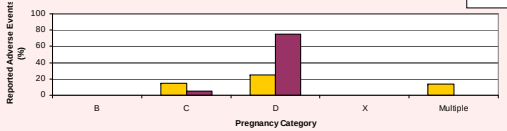
Reported Adverse Events in Animals and Humans



Animal data: Nonteratogenic and Teratogenic Effects



Human pregnancy data: Nonteratogenic and Teratogenic Effects



*Includes Adverse Event reports that were not defined as studies
*General class adverse events were not included unless the drug was specified

Conclusion & Future Works

Consistency Across Therapeutic Class

- Out of the 20 therapeutic classes surveyed, 9 (45%) were consistently labeled across class.

Consistency of Pregnancy Information within Pregnancy Categories

- One of the concerns about the current pregnancy labeling system is that drugs within the same category have a similar potential to cause toxicity. The information obtained from this study further emphasizes that point since the information presented in pregnancy labels varied within pregnancy categories.
- The majority of drugs in this study were classified Pregnancy category C (60%).
- Human studies done in pregnant women are rare across all pregnancy categories which may be attributed to ethical concerns. (Category B reported 4%, Category C reported 11%, Category D reported 25%, Category X reported 25%, and the Multiple category reported 14%).
- In addition to Pregnancy labels, Pregnancy Registries also provide important information regarding the safety of medication use. Category B reported 8%, Category C reported 12%, Category D reported 50%, and Category X and Multiple reported 0%. .
- Category C had the highest percentage of animal studies conducted with the multiple category having the lowest.

Future

- Comparison of data from various epidemiologic studies with data from pregnancy registries
- In response to the need to update the current labeling system the FDA has proposed a new pregnancy and lactation labeling rule which would replace the current labeling system with a narrative while phasing out the current letter categories.

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