# ADVERSE DRUG REACTIONS AND MEDICATION ERRORS

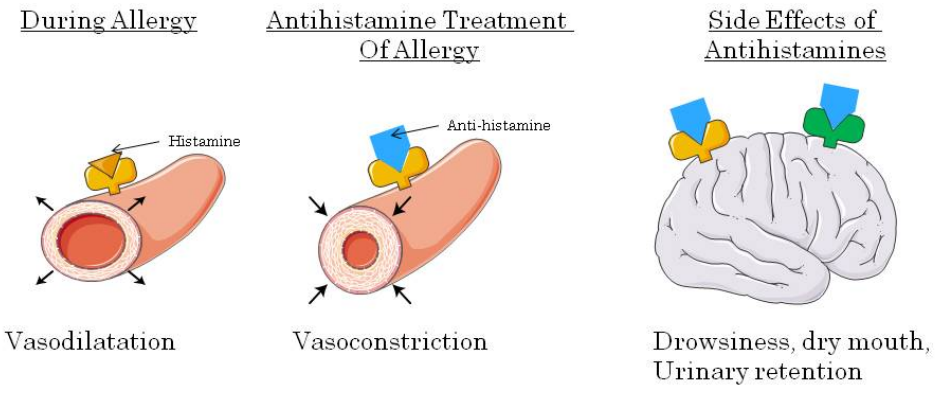
## 10.1 Adverse Drug Reactions

- Adverse drug reactions (ADRs) are the unintended and undesired responses from drugs.
- Adverse drug reactions are an enormous societal health problem.
- Canadian research suggests that 7.5% of hospital admissions in Canada are attributed to adverse drug reactions. This represents 185,000 people per year!
- Adverse drug reactions can include:

1. Side effects
2. Drug toxicity
3. Allergic Reaction
4. Idiosyncratic Reaction
5. Carcinogenic Effects
6. Mutagenic Effects
7. Teratogenic Effects

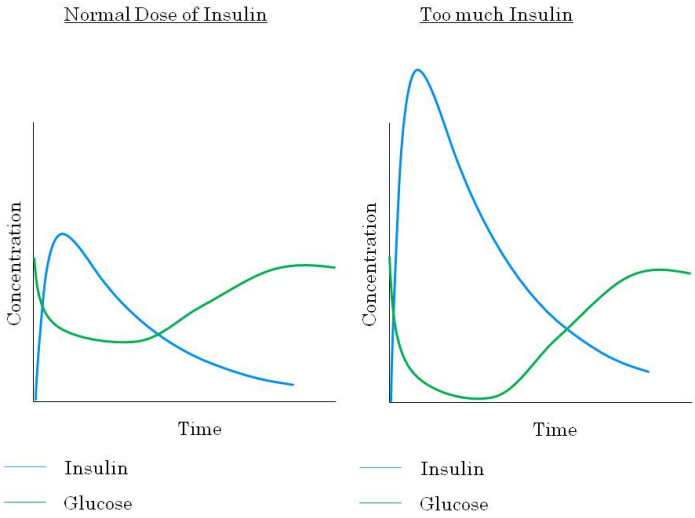
1. <u>Side effects</u>

- Side effects are secondary to the main therapeutic effect of the drug and are expected.
- Side effects occur at normal therapeutic doses and are often unavoidable.
- Side effects are often due to poor specificity or selectivity of the drug.
- Example: antihistamines act by blocking H1 histamine receptors to prevent the symptoms of allergy (i.e. runny nose, watery eyes). Side effects include drowsiness, dry mouth and urinary retention. In the figure you can see that histamine binding to the histamine receptor in sinuses causes vasodilation which results in runny nose and watery eyes. Antihistamines act by blocking the effect of histamine. Side effects occur when antihistamines bind to either histamine receptors or other receptors in the brain. This produces sedation, dry mouth and urinary retention. These are side effects of antihistamines.



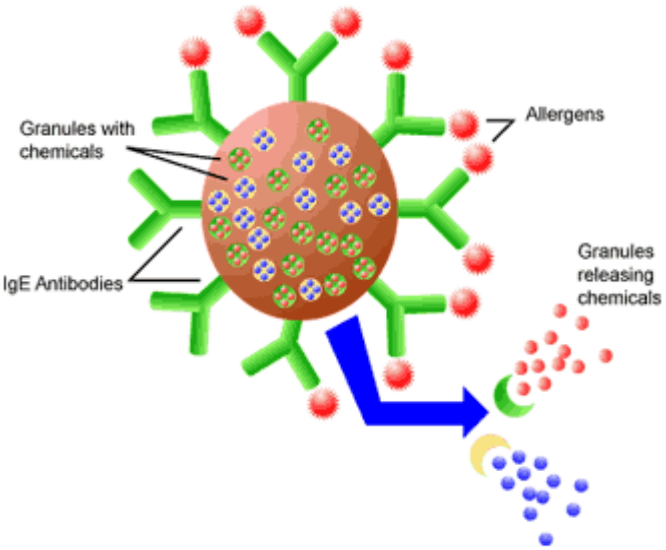
2. Drug toxicity

- Drug toxicity can be considered as any severe adverse drug event.
- Drug toxicity is often mediated by overdose where patients unintentionally or intentionally take too much medication.
- These types of reactions are often extensions of the therapeutic effect.
- For example, a patient who takes too much insulin will experience hypoglycemia (low blood glucose).

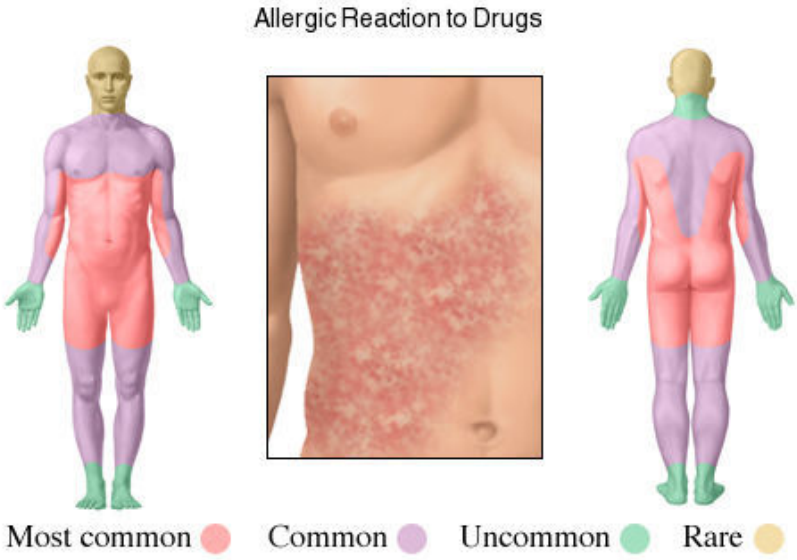



3. Allergic Reaction

- Allergic reactions are mediated by the immune system.
- Allergy requires a prior sensitization where a patient is exposed to the allergen (i.e. drug).
- Upon subsequent exposure to the drug an allergic reaction will occur. During allergic reactions, mast cells release chemical mediators such as histamine.
- Allergic reactions can vary from itching and rash, to life threatening anaphylaxis (bronchospasm, edema and severe hypotension).




- The intensity of allergic reactions are independent of dosage size. Therefore small doses can produce severe allergy.
- ~ 10% of all ADRs are related to drug allergy.
- Very few drugs cause allergic reactions. The most common drug class to cause drug allergy are the penicillins. Sulfonamides (an antibiotic) and nonsteroidal anti-inflammatory drugs (NSAID) are also known to cause drug allergy.



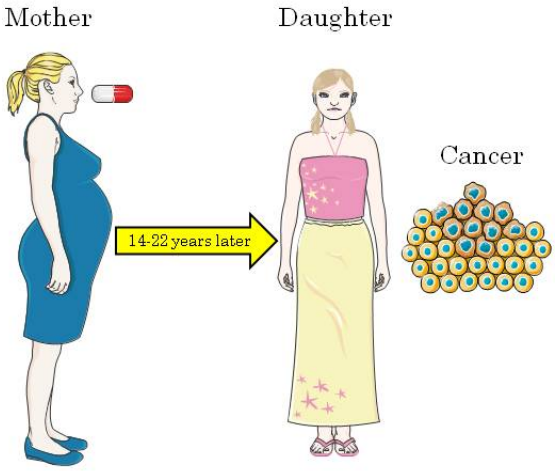

4. Idiosyncratic Reaction

- These are reactions that occur rarely and unpredictably in the population.
- Recent evidence suggests that genetic polymorphisms account for the majority of idiosyncratic reactions.
- The majority of polymorphisms causing idiosyncratic reactions occur in drug metabolizing enzymes and drug transport proteins.
- It is hoped that one day, routine blood test will be able to determine people at risk for idiosyncratic reactions due to genetic polymorphisms. This already occurs in some centres for the drugs warfarin and 6-mercaptopurine which are metabolized by CYP2C9 and thiopurine methyltransferase (TPMT) respectively.

Example of genetic polymorphisms that cause idiosyncratic reactions:

A. CYP2C9 – Approximately 15% of Caucasians have a polymorphism that decreases metabolism.
B. CYP2D6 – 10% of Caucasian and African Americans are poor metabolizers. These patients do not experience pain relief when they take codeine. Codeine is a prodrug that is metabolized by CYP2D6 to morphine.
C. Thiopurine methyltransferase (TPMT) – Approximately 10% of patients have decreased activity and 0.3% have no activity. Treatment with thiopurine drugs in patients with low or absent TPMT can result in life threatening bone marrow suppression.
D. OATP1B1 – An uptake drug transporter in the liver. 15% of Asian and Caucasian patients have a polymorphism that decreases function. This leads to an increase in plasma drug concentrations. This polymorphism has been implicated in causing myopathy (muscle toxicity) in patients taking statin drugs.
E. Glucose 6-Phosphate dehydrogenase deficiency (G6PDH) – An enzyme important in red blood cell metabolism. Deficiency is common in people of African and Middle Eastern descent. Patients with deficiency may have red blood cell hemolysis following treatment with certain analgesics (i.e. Aspirin) or anti-malarial drugs.

5. Carcinogenic Effects




- Carcinogenic means the ability of a drug to cause cancer.
- Relatively few drugs are carcinogenic.
- Determining whether a drug is carcinogenic is difficult because it normally takes years after the initial dose to appear.
- The drug diethylstilbestrol (DES) used to be prescribed to prevent spontaneous abortion in high risk pregnancies. Years later it was determined that the female offspring developed vaginal or uterine cancer.

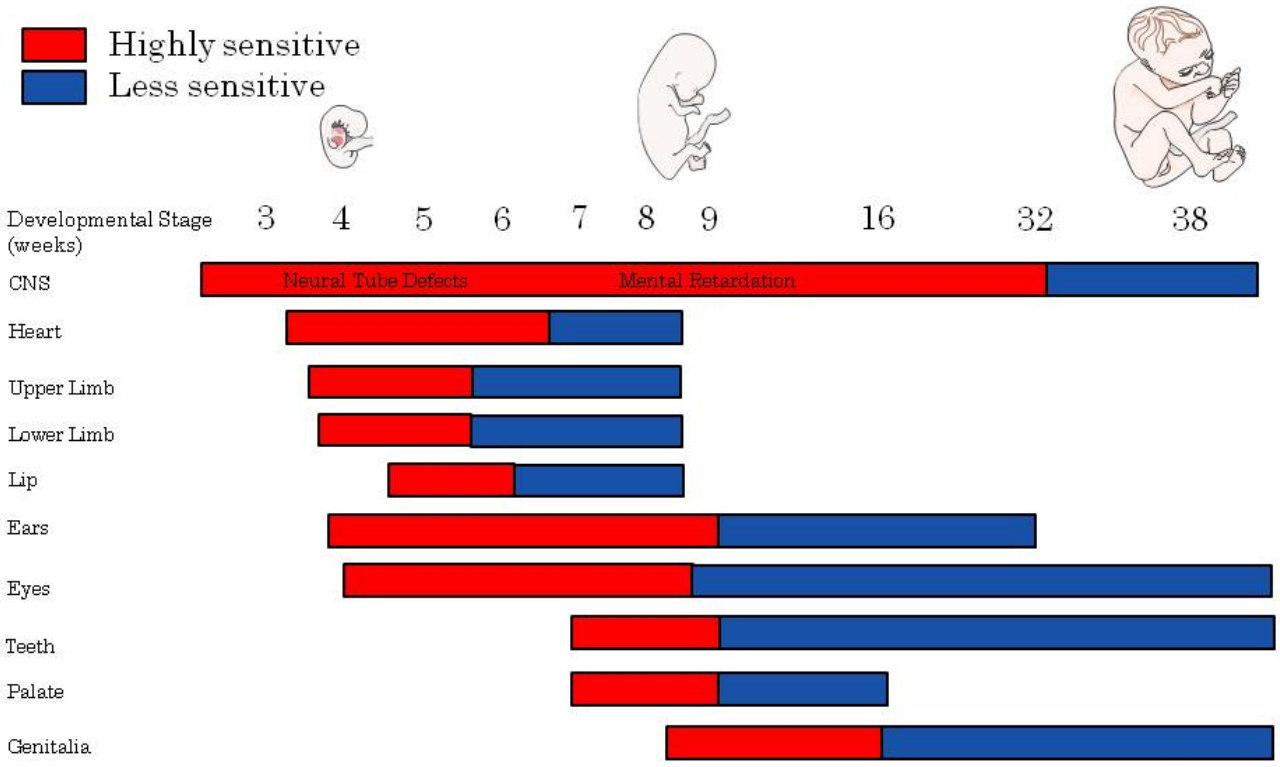
6. Mutagenic Effects

- If a drug is mutagenic it is able to change DNA.
- Often when a drug is mutagenic it is also carcinogenic or teratogenic.
- Sometimes drugs that are mutagenic are not carcinogenic or teratogenic. These drugs may receive approval for use from regulatory agencies if there is sufficient evidence of safety from preclinical studies.
- Drugs are tested for their potential as mutagens by the Ames test.
- The Ames test evaluates the ability of the test compound (i.e. a drug) to cause a mutation in specialized strains of bacteria.

7. Teratogenic Effects

- Compounds that are teratogens are known to produce birth defects or impair fertility.
- Typically we think of birth defects as major physical malformations, but birth defects also include behavioural and metabolic defects.
- Less than 1% of all birth defects are caused by drugs.
- Sensitivity to teratogens changes during development.
- Gross malformations typically occur when exposure to a teratogen is in the 1$^{st}$ trimester.
- Teratogen exposure during the second and third trimesters usually disrupts function as opposed to gross anatomy.
- Transfer of drugs across the placenta is thought to be greatest in the third trimester because as the placenta develops, the surface area for transfer between maternal and fetal circulation increases. In addition, the placental-fetal barrier becomes progressively thinner.
- The United States Food and Drug Administration has categorized drugs according to their risk. In Canada we use the American table as a guideline.

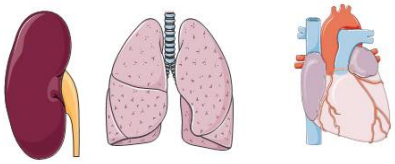
## Teratogenesis by Developmental Stage

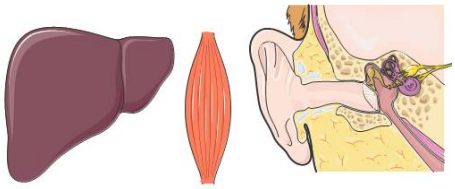



## Pregnancy Risk Categories

| Category | Description |
|---|---|
| A | •Well controlled human studies have failed to show risk to the fetus during the 1st trimester<br>•no evidence of harm later in pregnancy. |
| B | •Animal reproduction studies have failed to show harm to the fetus and there are no well controlled studies in pregnant women, OR<br>•Animal studies have shown an adverse effect but well controlled studies in pregnant women fail to show any harm. |
| C | •Animal studies have shown harm to the fetus but there are no well-controlled studies in pregnant women.<br>•Potential benefits of the drug outweigh the potential risk. |
| D | •Clear evidence of risk to the fetus from studies in humans.<br>• Potential benefits of the drug outweigh the potential risk. |
| X | •Studies in animals and humans clearly demonstrate risk to the fetus.<br>•Risks of using the drug clearly outweigh the benefits.<br>•These drugs should never be used in pregnant women. |

## 10.2 Organ Specific Toxicity

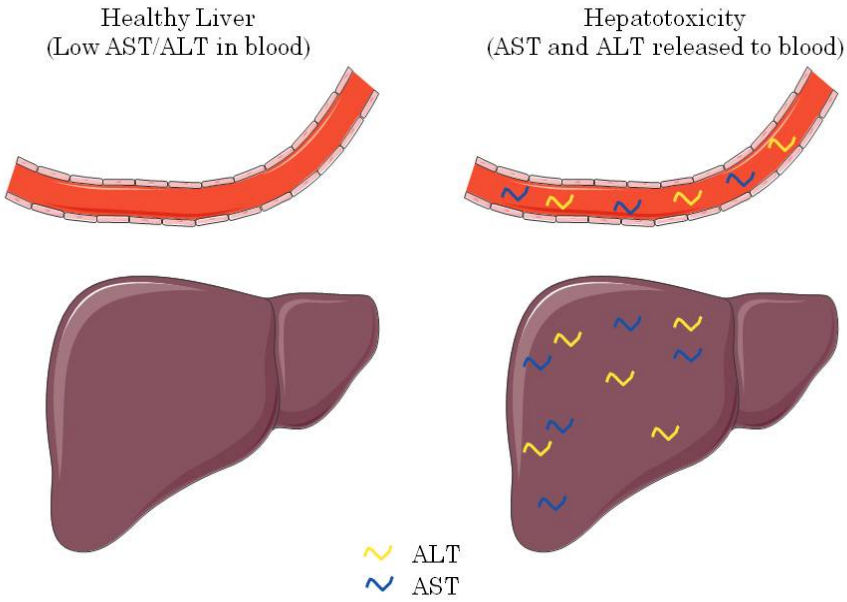




- Many drugs exhibit toxicity to a specific organ.
- Organ specific toxicity can occur to the kidney, lung, heart, liver, muscle and inner ear amongst others.
- The most common and important organ specific toxicity is observed in the liver and heart.

**Hepatotoxicity**

- Hepatotoxicity is the most common reason for an approved drug to be removed from the market.
- Why? Remember the liver is the primary site of drug metabolism. Some drugs are metabolized to toxic metabolites which can then cause liver injury.
- Several drugs known to be hepatotoxic are administered to patients.
- All patients taking hepatotoxic drugs should be educated to look for signs of liver toxicity which include: jaundice (yellow skin), dark urine, light-coloured stool, nausea and vomiting.

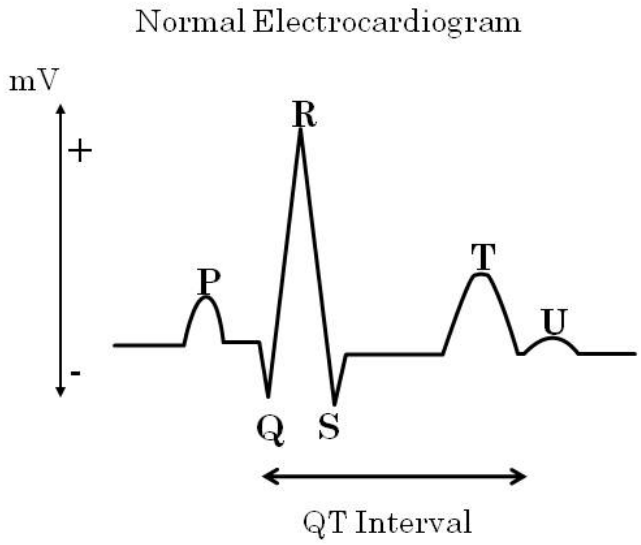



- In addition, liver function tests should be performed by measuring blood levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
- AST and ALT are liver enzymes that normally have a low concentration in the blood. When the liver is damaged, blood concentration of these enzymes increases.
- Drugs known to be hepatotoxic should be used with caution in patients at high risk for hepatic disease (alcoholics), patients with hepatic disease, and patients taking other medications with known hepatotoxicity.

**QT Interval Prolongation**

- The electrocardiogram (ECG or EKG) shows the electrical activity of the heart. An ECG is obtained by placing electrodes on the skin and measuring the electrical activity that occurs with each heartbeat.
- Each "bump" in the ECG represents a different event in the heart beat.

P-Wave: normal atrial depolarization.
QRS complex: rapid depolarization of the left and right ventricles.
T-Wave: repolarization of the ventricles.
U Wave: not always seen on an ECG.
QT Interval: Represents the time required for the ventricles to repolarize. A prolongation of the QT interval is a major risk factor for the development of *torsades de pointes*, a life threatening form of ventricular arrhythmia.




- More than 100 drugs are known to prolong the QT interval and many have been removed from the market.
- Drugs that prolong the QT interval should be used with caution in patients predisposed to arrhythmias such as the elderly, and patients who have bradycardia (slowed heart beat), heart failure, low potassium or congenital QT prolongation.
- Women are at higher risk than men because their normal QT interval is longer.

**Drug Withdrawal**

- So far we have only discussed adverse drug reactions associated with administering medications. What about when we take medications away?
- Some medications must be withdrawn slowly to prevent adverse reactions.
- An important part of patient education is to make sure that patients understand that they cannot simply stop taking a medication because they feel better. In some cases this can have drastic consequences.

| Class of Drug | Therapeutic Use | Consequence of Rapid Withdrawal |
|---|---|---|
| Opiates | Analgesia (Pain relief) | Anorexia, irritability, nausea, vomiting, weakness, muscle spasm. |
| Benzodiazepines | Anxiety | Anxiety, insomnia, sweating, tremours, panic, delirium, paranoia, convulsions. |
| Beta Blockers | Hypertension, Decrease Heart Rate | Rebound hypertension, chest pain myocardial infarction, arrhythmia. |

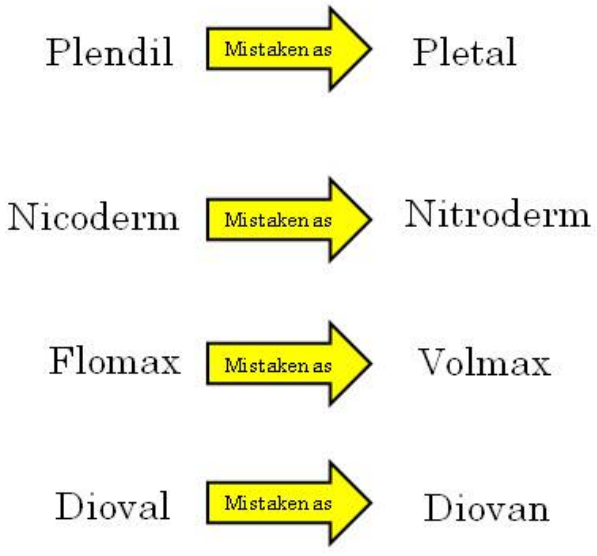
## 10.3 Medication Errors

- Medication errors are the most common cause of adverse drug reactions.
- If a medication error is caused by a health care professional it is called an iatrogenic error.
- Medication errors can be broken up into 5 main categories:

1. Prescribing – Health care professional prescribes the wrong drug, wrong dose or wrong route.
2. Dispensing – The prescription is correct but the pharmacist dispenses the wrong drug.
3. Administration – The health care professional administers the incorrect dose and/or drug. Note, a patient can also make this error.
4. Patient education – Illiteracy or language barriers may cause the patient to not comprehend the instructions. The health care professional (doctor, nurse and pharmacist) must work together to ensure all patients understand information about drugs.
5. Patient – The patient understands the instructions but doesn't follow them (i.e. misses doses, takes more medication than prescribed).

**Drug Naming**

- Unfortunately the naming of many drugs are similar.
- Medication errors are likely to occur when drug names look and/or sound the same.
- Confusion over drug names represents ~ 15% of all medication errors.
- Poor handwriting, illiteracy and strong accents (english as a second language) increase the chance of this type of medication error.
- The diagram shows some common drug naming errors.



**Abbreviations**

- Abbreviations can be dangerous sources of errors.
- The Institute for Safe Medication Practices has put together a list of error prone abbreviations (http://www.ismp.org/tools/errorproneabbreviations.pdf).
- This is an American source but is definitely relevant to Canadian health care.
- The table shows abbreviations that must be avoided in clinical practice.

Error Prone Abbreviations that MUST be avoided

| Abbreviation | Intended Meaning | Misinterpretation | Preferred Alternative |
|---|---|---|---|
| IU | International Unit | Misread as IV or "10" | Write "Units" |
| q.d | Every day | qid – tail of "q" and period read as "i" | Write "every day" |
| q.o.d | Every other day | Mistaken as q.d. Or q.i.d. | Write "every other day". |
| Trailing "0" after decimal point (i.e. 1.0 mg) | 1 mg | Mistaken as 10 mg if decimal is missed | Do not use trailing zeros for doses expressed in whole units. |
| Leading "0" before a decimal point (i.e. .5 mg) | 0.5 mg | Mistaken as 5 mg if decimal is missed. | Use a zero before a decimal place when the dose is less than a whole unit. |
| $MgSO_4$ | Magnessium Sulfate | Morphine sulfate | Write "magnessium sulfate" |
| MS, MSO4 | Morphine Sulfate | Magnessium Sulfate | Write " Morphine Sulfate" |