

Acetaminophen and Liver Injury

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Course Objectives

When you finish this course, you will be able to:

- Identify acetaminophen (Tylenol) and its use in combination drugs.
- Discuss the causes of unintentional acetaminophen overuse and overdose.
- State the signs and symptoms of liver injury from acetaminophen overdose.
- Distinguish safe potencies of acetaminophen preparations for infants, children, and adults.
- Identify populations at high risk for adverse effects from Tylenol overdose.
- Describe current FDA recommendations for acetaminophen use.

Introduction

Millions of people use over-the-counter (OTC) pain relievers every day to treat minor aches and pains. Usually these medicines are safe and effective, but they can be dangerous and even deadly when they are not taken as directed. That is particularly important with acetaminophen, an active ingredient in many OTC and prescription medicines that are used to relieve pain or reduce fever. Acetaminophen is generally safe at recommended doses, but if you take more than that, even just a little more, it can cause serious and even fatal liver damage. In fact, acetaminophen poisoning is a leading cause of liver failure in this country (FDA, 2009a).



Open bottles of Extra Strength Tylenol and Extra Strength Tylenol PM, pain relievers with the active ingredient acetaminophen/paracetamol. Tylenol PM (the white-and-blue tablets) also contains diphenhydramine, a sleep aid. From: Wikimedia.org.

Acetaminophen's effectiveness in relieving pain and fever is widely known. It is the generic name of a drug found in hundreds of OTC products including Tylenol, cough and cold medicines and sleep aids, as well as prescription pain relievers such as Vicodin and Percocet. However, it is not always clear to the consumer that these medications contain acetaminophen. If more than one medication is taken that contains this drug, consumers may inadvertently take more than the recommended dose. Because the risks of acetaminophen-related liver damage are so serious and because the public is often unaware of these risks, in April 2009 a Food and Drug Administration (FDA) advisory panel issued new rules governing its use (Regulations.gov, 2009).

The new rules issued by the FDA came after many years of discussion about acetaminophen's ability to cause liver damage. The final rulings strengthen warning labels on OTC acetaminophen and acetaminophen-containing products. The FDA also convened a public advisory committee meeting in June 2009 regarding acetaminophen use in both OTC and prescription products to consider further interventions to reduce the incidence of liver injury. Main (2009) reports:

“Thirty-two years ago, the FDA recommended that there be strong warnings on acetaminophen products, and those recommendations were finally put in place three months ago,” says Sidney M. Wolfe, MD, director of the Health Research Group of Public Citizen and the consumer representative on the FDA advisory panel. “Huge numbers of people have died from acetaminophen liver toxicity, and they wouldn't have if the FDA had moved on its recommendations.”

What Is Acetaminophen?

Acetaminophen, the active ingredient in Tylenol, is also known as paracetamol and N-acetyl-p-aminophenol (APAP) and has been marketed in the United States as an OTC antipyretic (fever reducing) and analgesic (pain reducing) agent since 1960 (Mayhew, 2007). Acetaminophen is widely available in a variety of strengths and formulations for children and adults as a single-ingredient product. It can also be found in combination with other active ingredients in what are called **combination medicines** that treat symptoms of colds and flu, allergies, and sleeplessness. Acetaminophen is also an ingredient in many combination prescription narcotic drugs such as Vicodin and Percocet. In the United States it is available as 325 milligram (mg) and 500 mg preparations and as a 650 mg extended-release medication intended for arthritis treatment. It comes in many forms including drops, capsules, and pills, as well as various children's dissolvable, chewable, and liquid formulations (Farrell, 2009).

Chemically, acetaminophen is a para-aminophenol derivative that is also the active metabolite of the analgesic drug phenacetin. Its effectiveness as an antipyretic agent is due to its effect on the brain's hypothalamic heat center, while its analgesic effect is due to its ability to raise the pain threshold (FDA 2004). It is quickly absorbed from the gastrointestinal tract, with peak plasma levels occurring between 30 and 60 minutes after the drug is taken at therapeutic levels. Peak plasma levels occur within 4 hours when an overdose is consumed (Powell, n.d.).

Recommended Doses

Although the FDA is considering decreasing the maximum recommended dose of acetaminophen, the currently recommended dose for adults and children over 12 years of age is 650 mg to 1000 mg every 4 to 6 hours as needed, but not to exceed 4000 mg in a 24-hour period. The recommended dose of extra-strength acetaminophen (which contains 500 mg per tablet) is 1000 mg every 4 to 6 hours (Powell, n.d.).

Two extra-strength acetaminophen tablets taken more than 4 times a day will produce an overdose, and it only takes a few days of exceeding the maximum dose to cause liver damage. If the patient also consumes alcohol, the risk of damage increases further (Mayhew, 2007). Because of this increased risk, the maximum dose of acetaminophen for a person who consumes more than two alcoholic drinks a day should be decreased to 2 grams per day (Lee & Marks, 2007).

Pediatric doses are based on age and weight, usually 10 to 15 mg per kilogram (kg) of body weight for a single dose and no more than five doses in a 24-hour period (Rx List, 2007). The

maximum recommended dose of extended-release acetaminophen is 1300 mg every 8 hours. Acetaminophen extended-release, extra-strength and arthritis formulas are not recommended for children less than 12 years of age (Powell, n.d.).

Acetaminophen Use

Acetaminophen is the most widely used analgesic medication in the United States despite its potential for hepatotoxicity. Over the past five years, the use of combination prescription products has increased dramatically, and is the biggest cause of acetaminophen overdose (Foxhall, 2009).

In 2005 American consumers purchased more than 28 billion doses of products containing acetaminophen, of which:

- Single-ingredient OTC products (eg, Tylenol) represented 8 billion doses.
- Combination OTC products (eg, NyQuil, Theraflu), represented more than 9.7 billion doses.
- Acetaminophen-containing prescription narcotics represented 11 billion doses.

Between 2001 and 2005, use of these combination prescription products increased 38%. There were more than 182 million prescriptions for combination prescription products in 2005 and the most frequently used acetaminophen-containing prescription product is Vicodin (hydrocodone/acetaminophen combination). It has been the most frequently dispensed prescription drug since 1997 (FDA, 2009b).

One recent study showed that of all the acetaminophen-caused acute liver failures (ALF), about 42% were due to patients intending self-harm and 48% were due to overdoses that were unintentionally taken (Foxhall 2009). Another study by the Acute Liver Failure Study Group (see below) found that nearly 50% of ALF occurrences were due to acetaminophen overdose (Lee & Larson, 2009).

Etiology of Acute Liver Failure (ALF) in the United States*

Cause	Incidence
Acetaminophen	605 (46%)
Drug related	156 (12%)
Hepatitis B	102
Hepatitis A	34
Autoimmune disorder	78
Ischemia	61
Wilson disease	19
Budd-Chiari syndrome	12
Pregnancy	11
Other	63
Indeterminate	180 (15%)

*Adult Registry; n = 1,321

Source: Adapted from: Lee & Larson, 2009.

Unintentional Acetaminophen Overdoses

Limited data are available that describe consumer behavior with acetaminophen products or consumer understanding of its toxicity. However, based on the prevalence of liver injury, it appears that there are distinct factors associated with acetaminophen and acetaminophen products that contribute to this public health problem (FDA, 2009b).

Consumers often do not know that taking more than the recommended dose of acetaminophen will not provide more relief and that they are in danger of liver damage if they exceed the maximum recommended dose. Despite warning labels, many consumers are unaware that alcohol exacerbates the risk of liver damage. Also, they may not realize how much acetaminophen they are consuming if they take more than one product containing this drug. Because acetaminophen is found in so many prescription and non-prescription products, taking more than the recommended dose is easy to do. People taking these medications may not even recognize that some of the drugs they are taking contain acetaminophen (FDA, 2009b).

Acetaminophen has a narrow safety margin and taking just a small amount of the drug over the traditionally recommended total daily dose (4 grams per day) may lead to liver injury. The recommended doses and tablet strengths of acetaminophen leave little room for error, and the onset of liver injury can be hard to recognize. There is scientific agreement that taking a large

amount of acetaminophen over a short period of time causes liver injury, but there are varying views on the specific threshold for toxicity (FDA, 2009b).

Some people may be especially prone to liver injury from acetaminophen, and the maximum amount of acetaminophen that can be safely ingested may not be the same for everyone. Some individuals, especially those who use alcohol or have liver disease, may have a greater susceptibility to the effects of the toxic metabolite produced by the breakdown of acetaminophen because they produce more of the metabolite or because they are unable to clear it from the body as easily as a healthy person. Individuals with increased susceptibility may experience toxic effects at lower acetaminophen doses than others and rare cases of acute liver injury have been linked to amounts lower than 2.5 grams per day. More research is needed to understand whether ethnicity, genetics, nutrition, or other factors might also play a role in making some individuals more prone to liver injury (FDA, 2009b).

Because there is such a wide array of OTC and prescription acetaminophen products used in a range of doses for various indications, it can be difficult to identify the appropriate product to use or how much of the drug is being ingested. Acetaminophen is an ingredient in many widely used OTC single-ingredient products, such as those used to treat headaches, and multiple-ingredient (combination) products, such as those that treat symptoms of the common cold.

As noted earlier, acetaminophen is also a component of a number of prescription drug products in combination with narcotic pain medicines. So, consumers may attempt to treat different conditions or symptoms with multiple choices among products containing acetaminophen, not realizing that acetaminophen is an ingredient common to each and that they are at risk of an overdose (FDA, 2009b).

In addition, it can sometimes be difficult to identify acetaminophen as an ingredient. Prescription products that contain acetaminophen (usually with codeine or oxycodone) are often labeled as containing "APAP" (N-acetyl-p-aminophenol), which is the active compound in acetaminophen. Not knowing what APAP is, patients may take more than one product containing acetaminophen (eg, a prescription product and an OTC product) and unintentionally take a harmful overdose. In a study published in the *Journal of the American Pharmacists Association* in 2007, 104 adult patients presenting to an internal medicine clinic were surveyed. Seventy-nine percent reported using a product that contained acetaminophen within the previous six months, but only 43% could identify problems that could arise from high doses of acetaminophen. And while 71% of patients recognized that Tylenol contains acetaminophen, fewer than 15% knew that **Vicodin** (hydrocodone/acetaminophen), **Darvocet** (propoxyphene/napsilate), and **Percocet** (oxycodone/acetaminophen) **contain acetaminophen** (FDA, 2009a).

Accidental overdoses can also occur in children because of the multiple products available that contain different strengths of acetaminophen. Liquid acetaminophen formulations intended for use in infants are typically more concentrated (ie, stronger) to enable proper dosing using less liquid. However, failure to distinguish between the two strengths of the liquid product can result in an overdose if a parent gives a higher dose of the concentrated infant drops to a young child (FDA, 2009c).

The association between acetaminophen and liver injury is not common knowledge. Consumers are not sufficiently aware that acetaminophen can cause serious liver injury, and their perceptions may be influenced by the marketing of the products. Because acetaminophen has been marketed

for decades, it is a familiar product that may be assumed to be completely safe. This perception may be reinforced by the fact that the drug is widely available OTC in very large quantities (eg, 500 tablets per bottle). Furthermore, advertisements of OTC products are not required to provide warning information (FDA, 2009b).

If too much acetaminophen is consumed, it can often be difficult to recognize the onset of liver injury. The onset of symptoms associated with acetaminophen liver injury can take several days, even in severe cases. In addition, symptoms may be non-specific and mimic flu symptoms, resulting in continued use of acetaminophen and further liver damage (FDA, 2009b).

Finding ways to educate consumers about the risk of liver injury from acetaminophen has been difficult. Current labeling on OTC products may be overlooked, as can the patient information provided with dispensed prescriptions. Programs to educate the public about safe use of acetaminophen have been small and encountered a number of obstacles. Advertisements of OTC drugs often emphasize the effectiveness of products but, unlike prescription drugs, are not required to offset such messages with warning information (FDA, 2009b).

Many factors contribute to unintentional acetaminophen overdose:

- The recommended daily doses and tablet strengths leave little room for error (FDA, 2009b).
- Some people have a decreased ability to clear the toxic metabolite created by the breakdown of acetaminophen.
- There are many medicines containing acetaminophen in a wide range of products and doses that make it difficult to know how much is being consumed.
- It is sometimes difficult to identify acetaminophen as an ingredient (eg, it is sometimes labeled as APAP).
- The majority of consumers do not know the dangers of acetaminophen.
- The symptoms of acetaminophen toxicity and liver damage may be difficult to recognize (FDA, 2004).

In children, these additional factors contribute to unintentional overdoses:

- Administering the wrong pediatric acetaminophen formulation (ie, substituting the concentrated infant drops for the less concentrated children's suspension).
- Administering the adult instead of the age-appropriate dose.
- Incorrectly calculating the weight-appropriate dose of acetaminophen.
- Using the wrong dosing device (eg, using a tablespoon instead of a teaspoon, or a dropper instead of a syringe) (FDA, 2004).

Liver Injury

Research has shown that acetaminophen is a major cause of acute liver failure in the United States. Taking more than the recommended amount of acetaminophen can cause liver damage ranging from abnormalities in liver function blood tests to liver failure and even death. There are an estimated 400 deaths each year from acetaminophen-caused liver failure (FDA, 2009a).

Acute liver failure (ALF) due to acetaminophen overdose:

- Accounts for approximately 50% of all cases of ALF
- Causes several hundred deaths in the United States annually
- Is the most common form of ALF in the Western world
- Is commonly unintentional rather than suicidal
- Outweighs all other drugs combined (Lee & Larson, 2009)

Liver failure caused by acetaminophen in intentional overdose situations or when used in combination with alcohol has been recognized for many years. In a study that combined data from twenty-two specialty medical centers in the United States, acetaminophen-related liver injury was the leading cause of ALF for the years 1998 through 2003 (FDA, 2009a).

Of 1600 cases of ALF in 2007, acetaminophen toxicity was again the most common etiology (FDA, 2009a). Patients in these studies were found to have taken too much acetaminophen from OTC, prescription products, or both. Almost half of these cases involved an overdose in which the patient had not intended to take too much acetaminophen (unintentional overdoses), although many cases of liver injury with acetaminophen result from intentional self-poisoning (FDA, 2009a).

Liver Injury, Population Overall

Summarizing data related to acetaminophen-associated overdoses from five different surveillance systems during 1990–1998, there were an estimated:

- 56,000 emergency department visits per year
- 26,000 hospitalizations per year
- 458 deaths per year

From 1998 to 2003, acetaminophen was the leading cause of ALF in the United States, with 48% of acetaminophen-related cases associated with accidental overdose. A 2007 CDC population-based report estimates that, nationally, there are 1600 cases of ALF each year (all causes).

Acetaminophen-related ALF was the most common etiology.

Source: FDA, 2990b.

The liver helps break down and remove many chemicals or drugs that enter the body, but taking too much acetaminophen overloads the liver's ability to process the drug effectively (FDA, 2009a). The mechanism of liver injury is not related to acetaminophen itself, but to the conversion of small amounts of acetaminophen into a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI) (Lee & Marks, 2007). When acetaminophen is taken in therapeutic doses, this metabolite is safely broken down by the liver and then excreted in the urine.

However, when liver function is impaired (eg, in alcoholics), or if an excessive amount of acetaminophen is ingested, high concentrations of NAPQI accumulate and bind with liver proteins, causing cellular injury. The amount of toxic metabolite produced and the ability of the liver to remove this metabolite before it binds to liver protein influence the extent of liver injury (FDA, 2009b). The following may also lower the threshold for acetaminophen-caused hepatotoxicity:

- Anti-seizure medications, such as phenobarbital, phenytoin (Dilantin), and carbamazepine (Tegretol)
- The anti-tuberculosis drug isoniazid (INH, Nydrazid, Laniazid)
- The fasting state, or poor nutrition (Lee & Marks, 2007)

Signs and Symptoms

An overdose of acetaminophen can seriously damage the liver. The antidote to acetaminophen overdose, N-acetylcysteine (NAC), is most effective when given within 8 hours of ingesting acetaminophen and can prevent liver failure if given early enough. For this reason, it is absolutely necessary that acetaminophen poisoning be recognized, diagnosed, and treated as early as possible (WebMD, 2005).

Unfortunately, the signs and symptoms of liver damage may not be immediately apparent because they take time to appear, even in severe cases. The early symptoms of liver damage (eg, loss of appetite, nausea, vomiting), may be mistaken for the flu (FDA, 2009a).

Signs of liver disease include abnormally yellow skin and eyes, dark urine, light-colored stools, nausea, vomiting, and loss of appetite. Serious cases of liver disease may lead to mental confusion, and liver damage can develop into liver failure, coma, and death over several days (FDA 2009c).

Treatment

Plasma levels in an overdose of acetaminophen peak about four hours after ingestion. Acetaminophen levels are therefore usually ordered four hours from the time of ingestion, although treatment is begun immediately. Severe liver injury can be minimized if N-acetylcysteine (NAC) is administered within 8 to 10 hours after acetaminophen ingestion (Prostko, 2009).

Treatment may include stomach lavage to remove any unabsorbed tablets, then orally administered activated charcoal to absorb any drug remaining in the stomach. This is followed by administration of NAC, either orally or intravenously. Since charcoal will absorb NAC, another stomach lavage may be done prior to oral administration to remove the activated charcoal (Powell, n.d.).

If the acetaminophen plasma levels are high, the patient may need to be given maintenance doses of NAC. The loading dose is 140 mg per kilogram of body weight and the maintenance doses are 70 mg per kilogram of body weight every 4 hours for a total of 18 doses (Powell, n.d.).

The Safe Use of Acetaminophen

[This section is taken from FDA, 2009d.]

The FDA gives the following advice to consumers for the safe use of acetaminophen:

1. Read all the information given to you by your doctor. Read the information on the OTC “Drug Facts” label or on the prescription label and follow the directions.
2. Be sure you understand the following:
 - The dose, which is how much acetaminophen you can take at one time
 - How many hours you must wait before taking another dose of acetaminophen
 - How many doses of acetaminophen you can take safely each day
 - When to stop taking acetaminophen and ask a doctor for help
3. Never take more than directed, even if your pain or fever isn’t any better. Taking more acetaminophen than directed can put you at risk for liver damage.
4. Never take more than one medicine that contains acetaminophen. Check the active ingredients of all your medicines to make sure you are taking no more than one medicine containing acetaminophen at a time.

You can safely give acetaminophen to infants, children, and teenagers if you check the active ingredients in the other medicines that your child is taking (or that your child may take) to make sure they don’t contain acetaminophen. Your child should never be taking more than one medicine containing acetaminophen at a time.

The FDA recommends that parents:

1. Read all the information given by your child's doctor and read the information on the OTC "Drug Facts" label or on the prescription label and follow directions.
2. Choose the right medicine based on your child's weight and age. If a dose for your child's weight or age is not listed on the label, or you cannot tell how much to give, ask your pharmacist or doctor what to do. On OTC medicines, the Directions section of the "Drug Facts" label tells you:
 - If the medicine is right for your child
 - How much medicine to give
 - How many hours you must wait before giving another dose
 - When to stop giving acetaminophen and ask a doctor for help
3. Use the measuring tool that comes with the medicine. It will give the exact dose. If you do not have the right measuring tool, ask a pharmacist. Do not use a spoon that is meant to be used for cooking or eating. A spoon should not be used to measure medicine because it may give the wrong amount.
4. Never give more than one medicine that contains acetaminophen. If you give more, it could harm your child.
5. In order to prevent medicine accidents:
 - Keep a record of the medicines you give your child. Write down the dose and time when you give the medicine. This will help everyone who cares for your child know how much medicine your child has had and prevent the accidental administration of an extra dose.
 - Keep medicine where it cannot be seen or reached by children and pets; a locked box, cabinet, or closet is best.
6. If the pain or fever do not improve, talk to your doctor, nurse or pharmacist. Give the medicine only as directed and no more.

If too much acetaminophen is ingested, or if too much is given to a child, do not wait. Call 911 or Poison Control (1-800-222-1222) right away to find out what to do. The signs or symptoms of liver damage may not be noticeable for hours or even days after taking acetaminophen. By the time you notice changes, the liver damage may be severe and could lead to death.

Special Populations

Older adults, children, those who regularly consume alcohol, and people who take certain medications are at increased risk of overdose from acetaminophen.

Older Adults

Older adults are the largest users of prescription medications, yet with advancing age they are more vulnerable to adverse reactions to the medications they are taking, as well as to dosing errors. About 30% of hospital admissions of older adults are drug-related. In addition, after the age of 75, older adults have decreased comprehension of medication instructions (Hughes, 2008).

Poor vision is also a problem more common with age. One study showed that almost one-half of the older patients stated that they were not able to read the labels on the bottles due to poor eyesight, inability to read English, or small writing on the bottles (Hughes, 2008).

Poor cognition may lead to inability to follow medication regimens. The most common type of non-compliance is dose omission, but over-consumption is also a common mistake in older people (Hughes, 2008).

Older adults have narrow therapeutic windows and require close monitoring, especially when on multiple medications. A review of ED visits of patients 65 years and older found that more than 10% of the visits were related to an adverse drug event and more than 30% had at least one potential adverse drug interaction in their medication regimen (Hughes, 2008).

The American Geriatrics Society states that for most older people, the maximum 24-hour dose of acetaminophen is 4 g and the 24-hour maximum in older patients with hepatic insufficiency or a history of alcohol abuse is 50% to 75% of the usual, or 2 to 3 grams (Thompson, 2006).

Children

Acetaminophen is a standard treatment for pain and fever in children and is available OTC primarily in liquid form. Parents need to use caution when administering liquid acetaminophen. Although the FDA is considering standardizing liquid concentrations of acetaminophen, at present it comes in two strengths, a suspension for older children and a more concentrated infant drop formula that is 3 times stronger than the children's suspension. The different concentrations can lead to serious errors in dosing (FDA, 2009b).

A proposal being considered by the FDA would require manufacturers to include a measuring device, properly calibrated and clearly marked for product dosing in each package, making it easier for caregivers to give the appropriate dose. Parents are cautioned against giving any acetaminophen or cough and cold medications to children under 2 years of age without the advice of a healthcare provider (FDA, 2009b).

Prescription dosing errors are also common in children, and their smaller size makes them more vulnerable to these errors and less able to communicate signs and symptoms that indicate a problem. In a recent study, a total of 15% of the 22 most commonly prescribed medications for children appeared to have dosing errors, and the most frequently overdosed drugs were the four analgesics examined—acetaminophen with codeine, ibuprofen, naproxen, and oxycodone (AHRQ, 2009).

Alcohol and Acetaminophen

It has been known for many years that there is an increased danger of liver damage in people who regularly drink alcohol and take acetaminophen, even at recommended doses. Acetaminophen and alcohol are both metabolized by the liver, which may become overwhelmed if it has to deal with both drugs at the same time. An increased amount of the toxic metabolite NAPQI is produced, causing liver cell death (Highleyman & Franciscus, 2007).

Drug Interactions

Warfarin (Coumadin) is a drug that is often used to prevent blood clots after heart valve replacement and for a type of abnormal heart rhythm called atrial fibrillation. A new warning has been issued by the FDA about a possible interaction between warfarin and acetaminophen that may increase the risk of bleeding. Healthcare professionals need to consider this as a possible cause of an increase in their International Normalized Ratio (INR) for patients taking warfarin. The INR is used to measure the clotting tendencies of the blood. The warning label reads as follows: "Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin." This warning is required on all OTC acetaminophen products except those also containing NSAIDS, which have their own stomach bleeding warning (Federal Register, 2009).

The risk of increased bleeding is greater with higher doses of acetaminophen. The bleeding risk has been found to increase tenfold in people who were taking 28 or more regular-strength acetaminophen tablets per week, or the equivalent of 18 or more extra-strength tablets per week, compared to those taking warfarin and no acetaminophen (Worst Pills, Best Pills, 2009).

There have been a number of reports of liver damage involving a possible drug interaction between isoniazid, a medication used to prevent and treat tuberculosis, and acetaminophen. Isoniazid alone, especially as people get older, has been documented to cause liver damage. The combination of acetaminophen with isoniazid may increase this danger (FDA, 2009e).

The FDA advises people who are taking isoniazid for tuberculosis or who have a positive TB skin test and are using this drug, to consult with their physician before using acetaminophen or any combination product containing acetaminophen. They are advised to discuss alternatives to acetaminophen with their physician (FDA, 2009e).

People who take anti-seizure medications like phenytoin (Dilantin), phenobarbital, or carbamazepine (Tegretol) should consult a doctor before taking acetaminophen. These drugs can cause an increase in NAPQI formation by the acetaminophen and can therefore increase liver damage (Lee & Marks, 2007).

History of FDA Rulings

In 1977 the FDA published a report from its Advisory Review Panel that recommended the following warnings related to liver injury. “For products containing acetaminophen: Do not exceed the recommended dosage because severe liver damage may occur” (Federal Register, 2009). According to Peter Lurie, deputy director of Public Citizen’s Health Research Group, “For almost three decades, the FDA chose to ignore this wise advice” (Lurie, n.d.).

In a *Worst Pills Best Pills* newsletter, McNeil, the makers of Tylenol, “fought hard to persuade the FDA that ‘severe liver damage’ was an unnecessarily alarming statement for the official product label because, it maintained, the only people who suffered such injury had taken massive overdoses, usually in suicide attempts” (Malone & Larson, 2009).

In 1988 the FDA issued a proposed rule referred to as a “tentative final monograph.” In this proposed rule, they decided not to adopt the Panel’s 1977 recommended liver warning because they concluded that warnings need not include information on the specific injury to organs of the body caused by an acute overdose of a drug. However, a modified warning was proposed “because we believed consumers should know that prompt medical attention is essential if an acetaminophen overdose occurs” (FDA, 2009b). In the proposed rule, the following warnings related to liver injury were included:

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms (FDA, 2009b).

In 1998 the FDA published the following final rule that required labeling information for all OTC products containing acetaminophen:

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask a doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage (FDA, 2009b).

In 2002 the FDA convened an Advisory Committee meeting to discuss unintentional liver toxicity related to the use of OTC acetaminophen. The Advisory Committee recommended a specific liver toxicity warning and distinctive labeling on OTC packages so that products containing acetaminophen could be more easily identified. The FDA and drug manufacturers were also advised to educate consumers and health professionals about the risk of liver injury from acetaminophen (FDA, 2009b).

In early 2004 the FDA launched a public education campaign to help consumers use acetaminophen more safely; however, the campaign was small due to budgetary constraints. It was also limited by reluctance on the part of some commercial outlets to provide a venue for the FDA's message about acetaminophen toxicity because the product was sold or promoted in those outlets (FDA, 2009a).

In 2004 the FDA sent letters to every state board of pharmacy asking them to consider requiring labeling on containers of prescription products containing acetaminophen that would: (1) use the term acetaminophen, not APAP, (2) instruct patients to avoid concurrent use of other acetaminophen containing drugs, (3) instruct patients not to exceed the maximum daily recommended acetaminophen dose, and (4) instruct patients to avoid drinking alcohol during prescription use. The FDA was informed by the National Association of Boards of Pharmacy that, as of February 2008, no states had implemented regulations related to the request (FDA, 2009b).

In December 2006 the FDA issued proposed regulations for the labeling of OTC acetaminophen products and to increase public education. The FDA also proposed lowering the maximum adult daily dose to 3250 mg from 4000 mg. and limiting individual tablets to 325 mg. It was also recommended that combination products be eliminated (CDER, 2008).

In 2007 the Director of the FDA's Center for Drug Evaluation and Research (CDER) convened a multidisciplinary working group to continue to evaluate the issues associated with acetaminophen-related liver injury and consider additional steps the FDA could take to decrease the number of these cases. The working group considered detailed reviews of the issues from the Office of Nonprescription Products, the Office of Surveillance and Epidemiology, and the Division of Anesthesia and Analgesic and Rheumatology Drug Products as part of its deliberations. The Center Director and the Working Group decided to present the recommendations for public discussion prior to taking further action (CDER, 2008).

New FDA Final Ruling

In April 2009 the FDA issued a final rule that must be implemented by manufacturers within one year, strengthening the labeling for OTC products containing acetaminophen. The following box lists some of the final labeling requirements for OTC products containing acetaminophen, which includes more specific warnings about liver injury, the role of alcohol in increasing the risk of liver injury, and the importance of avoiding the use of more than one product that contains acetaminophen (FDA, 2009b).

Labeling Requirements for OTC Products Containing Acetaminophen, April 2009

- The alcohol warning is part of the liver warning (instead of the separate alcohol warning previously required).
- The warning includes information on the potential for severe liver damage associated with exceeding the maximum daily dose or taking three or more alcoholic drinks a day while taking acetaminophen.
- The liver warning is required on immediate container labels in addition to the carton or outer container.
- The ingredient name (acetaminophen) is highlighted or in bold type and in a prominent print size on the package's principal display panel (PDP) of the immediate container, and the outer carton (if applicable). This is intended to help consumers identify the active ingredient and reduce the number of people inadvertently exposed to multiple products containing acetaminophen.
- "See new warnings information" is highlighted or in bold type and in a prominent print size on the PDP. This statement must appear on the products PDP for one year after the final rule is published.
- The label must contain a warning not to use acetaminophen with any other drug containing acetaminophen and to ask a doctor or pharmacist if unsure. It must also include a direction to ask a doctor before taking acetaminophen in the presence of liver disease or if using the blood-thinning drug warfarin.
- The FDA will also expand its existing educational programs to reach both the general public and healthcare professionals in order to raise awareness about acetaminophen and liver injury and to encourage safe use practices. These educational programs will include:
 - Take no more than the recommended dose of acetaminophen.
 - Do not mix acetaminophen-containing products.

Talk to your doctor about acetaminophen if you consume alcohol or have liver disease.

Source: FDA, 2009b.

Recommendations for Future Rulings

(This section from FDA, 2009b)

The Center for Drug Evaluation and Research staff reviewed the interventions recommended by the acetaminophen working group to reduce the incidence of liver injury and developed options that were discussed at the Advisory Committee meeting in June 2009. “The FDA will evaluate the recommendations and assess whether there are regulatory pathways available to the agency to accomplish its goals and, if so, the advantages and disadvantages of each pathway. Such an evaluation, and implementation of selected options, will take some time” (FDA, 2009b). The following options will be considered by the FDA.

Option 1: Reduce current doses (eg, current maximum adult daily dose, single adult dose, and tablet strength).

Alternatively, restrict current maximum adult daily dose, single adult dose, and tablet strength to prescription only. Acetaminophen has a narrow safety margin. This means there is little difference between the maximum daily dose and a potentially harmful dose. This option involves reducing the amount of acetaminophen recommended as a daily dose for OTC, and perhaps also prescription products, to decrease the likelihood that patients will unintentionally exceed safe doses. Alternately, any amount of acetaminophen greater than 325 mg per tablet (650 mg recommended dose) could be restricted to prescription only.

Option 2: Establish package size limits for OTC acetaminophen products.

Today, consumers can purchase acetaminophen OTC from a variety of pharmacies and drug stores in a variety of package sizes, containing up to hundreds of doses. Limiting the number of acetaminophen doses (tablets, capsules, liquids) in a package and potentially introducing sales restrictions, might alert consumers to use acetaminophen safely and may be particularly useful in reducing the incidence of intentional poisonings associated with acetaminophen.

Option 3: Require unit-of-use packaging for prescription products.

Many products come to pharmacies in bulk, enabling the pharmacist to repackage to suit individual patient needs. Unit-of-use packaging means the product comes to the pharmacy packaged ready for sale without having to be repackaged. This proposal would enable the FDA to standardize the information laid out on the prescription label, warnings, and description of active ingredients (ie, acetaminophen instead of APAP). Armed with appropriate risk information, patients would be able to reduce the risk of unintentional overdose.

Option 4: Expand product warning information on prescription products.

The FDA recently issued new regulations for labeling OTC products containing acetaminophen. As a result, this option focuses primarily on improving prescription labeling. If all acetaminophen-containing prescription products were required to consistently and prominently identify acetaminophen as an ingredient (and not use different terms, such as APAP), it might be easier for consumers to identify this ingredient.

Option 5: Eliminate combination OTC and/or prescription products that contain acetaminophen.

Some prescription products and many OTC products contain acetaminophen along with other active ingredients. Consumers are not always aware when acetaminophen is present in these combination products and take them with other acetaminophen-containing products. Eliminating combination products that contain acetaminophen may reduce the risk of duplicate dosing.

Option 6: Limit dosing formulations for OTC liquid products; require dosing device.

Acetaminophen is available in liquid form primarily for children, but also for adults. Today, liquid acetaminophen comes in two strengths, a suspension for older children and a more concentrated liquid referred to as “infant drops.” Sometimes the availability of multiple strengths causes confusion when treating children. This option proposes that all liquid products be made in the same concentration. In addition, manufacturers would be required to include in each package a measuring device (spoon or container), properly calibrated and clearly marked for product dosing, making it easier for caregivers to give the appropriate dose.

Conclusion

Acetaminophen is one of the most commonly used drugs in the United States to reduce pain and fever. But, despite its undeniable popularity, efficacy, and general safety when used according to dosing instructions, acetaminophen is the leading cause of acute liver failure in this country (CDER, 2008). Although many instances of liver injury are the result of intentional overdoses, almost half of these events occur because patients unknowingly take too much of the drug.

Acetaminophen has a narrow therapeutic margin and there is little difference between the current maximum recommended dose of acetaminophen and the doses that are associated with an elevated risk of hepatotoxicity. Liver abnormalities caused by acetaminophen toxicity can range from abnormalities in liver function blood tests to acute liver failure and death.

The new rule issued by the FDA in 2009 came after many years of discussion about acetaminophen’s ability to cause liver damage. The final ruling strengthens warning labels on OTC acetaminophen and acetaminophen-containing products. The FDA also convened a public advisory committee meeting in June of 2009 regarding acetaminophen use in both OTC and prescription products to consider further interventions to reduce the incidence of liver injury.

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(Post Test begins on next page)

Post Test

Use the answer sheet following the test to record your answers.

1. Tylenol is sometimes known as:
 - a. Indomethacin.
 - b. APAP or paracetamol.
 - c. Naproxen.
 - d. Ibuprofen.

2. Tylenol is sometimes an ingredient in combination drugs, including:
 - a. Percocet and Vicodin.
 - b. Celebrex and Enbrel.
 - c. Lisinopril and benazepril.
 - d. Viagra and Cialis.

3. The current recommended maximum 24-hour dose of Tylenol is:
 - a. 1000 mg.
 - b. 2500 mg.
 - c. 4000 mg.
 - d. 6000 mg.

4. People who consume more than two alcoholic drinks per day should:
 - a. Not take Tylenol at all.
 - b. Take only NSAIDs for pain.
 - c. Take no more than 2 grams per day.
 - d. Consider rehab before taking any pain medications.

5. A recent study of acetaminophen-caused liver failure indicated that 48% were due to unintentional overdoses. A
 - a. True
 - b. False

6. Liquid Tylenol formulations for infants are:
 - a. Typically stronger than those intended for older children.
 - b. About the same strength as those intended for older children.
 - c. Not as strong as those intended for older children.
 - d. Different only from adult formulations.

7. The onset of liver injury:
 - a. Is immediately evident.
 - b. Becomes evident within a few hours.
 - c. Has easily identifiable symptoms.
 - d. Can take several days, even in severe cases.

8. Incidence of acute liver failure (ALF) due to acetaminophen overdose:
 - a. Accounts for most cases of ALF.
 - b. Generally results from intentional overdose.
 - c. Is negligible despite ongoing concerns.
 - d. Outweighs all other drugs combined.

9. The early symptoms of liver damage may be mistaken for the flu.
 - a. True
 - b. False

10. To treat overdose of acetaminophen:
 - a. Immediately administer fluids to dilute the volume of the drug in the bloodstream.
 - b. Wait 4 hours to determine peak plasma levels before proceeding.
 - c. Administer N-acetylcysteine (NAC) within 8 to 10 hours after ingestion.
 - d. Take measures to add the patient's name to the liver transplant list.

11. A child should never be given more than one medication containing Tylenol at the same time.
 - a. True
 - b. False

12. Older adults using Tylenol need special attention because:
 - a. They came of age during a time of increased interest in using drugs recreationally.
 - b. Poor vision or cognition may cause inability to follow medication regimens.
 - c. They rarely use OTC medications.
 - d. Dosages need to be higher because of common aches and pains.

13. People who take warfarin to prevent blood clots:
 - a. May be at increased risk for bleeding if they also take Tylenol.
 - b. Can also take Tylenol so long as they don't exceed the 24-hr maximum.
 - c. Will benefit by the addition of Tylenol and have even fewer blood clots.
 - d. May offset the benefits of the warfarin if they take Tylenol.

14. In 2009, the FDA's ruling on labeling of acetaminophen:
 - a. Found that no changes were necessary.
 - b. Mandated a 5-year waiting period for implementation of changes.
 - c. Included alcohol and liver warnings.
 - d. Applied only to combination drugs.

(Answer Sheet on next page)

Answer Sheet

Acetaminophen and Liver Injury

Name (Please print your name): _____

Date: _____

Passing score is 80%

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____
13. _____
14. _____

Course Evaluation

Please answer each of the following questions. Questions with asterisks (*) are required.

* 1. This course met the goals and learning objectives.

Yes No

* 2. The author was well prepared to write about the content in a way that facilitated my learning.

Yes No

* 3. This course was free from commercial bias.

Yes No

* 4. The learning activity met my continuing education needs.

Yes No

* 5. The learning activity took me 60 minutes per contact hour. (If you answer "No", please enter the total time it took to finish the course, test, and evaluation.)

Yes

No**

** If your answer was "No", how long did it take to finish the course, test, and evaluation?

6. My professional educational level is (check one):

Nursing

Nurse Aide LVN/LPN RN (diploma) RN (AD)

BSN MSN Nurse Practitioner / Advanced Practice Nurse

PhD / DNSc

Therapy

OT Aide COTA OT MOT OTD

PT Aide PTA PT MPT MSPT DPT PhD

Other (please specify): _____

(continued on next page)

7. I heard about ATrain Education from:

- | | |
|--|---|
| <input type="checkbox"/> Search engine | <input type="checkbox"/> Advertisement |
| <input type="checkbox"/> Government or Board website | <input type="checkbox"/> Returning customer |
| <input type="checkbox"/> Friend | <input type="checkbox"/> Publication (Magazine, etc.) |
| <input type="checkbox"/> Other _____ | |

8. I found the ATrainCEU.com website easy to use:

- Yes No

9. Comments or suggestions (optional): _____

(Registration information on next page)

Registration Information

Please answer all of the following questions (*required).

* Name: _____

* Address: _____

* City: _____ State: _____ Zip: _____

* Phone: _____

* Professional Designation: _____

* License Number and State: _____

Please e-mail my certificate: Yes No

Email (required if you want your certificate sent by email): _____

(Note: If you request an email certificate we will not send a copy of your certificate by US Mail.)

Payment Options

You may pay by credit card or by check. Fill out this section only if you are **paying by credit card**.

1.5 contact hours - \$12

Credit card information:

Name _____

Address (if different from above): _____

City: _____ State: _____ Zip: _____

Card type: Visa MC American Express Discover

Card number _____

Expiration date _____

Test Completion and Mailing Instructions

1. Complete all forms:

- Answer Sheet
- Evaluation Learning Activity
- Registration Form (this page)

2. If you are **paying by check**, prepare a check for \$12 made out to ATrain Education, Inc.

3. Mail the completed forms and your payment to:

ATrain Education, Inc
5171 Ridgewood Rd
Willits, CA 95490

Once we receive your forms and payment, we will mail (or email, if you request it) your certificate of completion. If you have any questions or concerns, please call or contact us at Sharon@ATrainCEU.com. And thanks for taking the ATrain!