

# Acetaminophen: When It Becomes Dangerous (239)

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Contact hours: 2

Course price: \$19

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## Course Summary

This course explores acetaminophen use and overuse with a focus on the signs and symptoms of liver injury and adverse effects. It also discusses FDA recommendations for various ages and at-risk populations.

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# Course Objectives

When you finish this course you will be able to:

- Explain the widespread use of acetaminophen both as an over-the-counter drug (OTC) and by prescription in combination with other drugs.
- Discuss self-dosing of acetaminophen as an OTC drug and the hazard of unintentional overdose.
- Describe the relationship of acetaminophen to acute liver failure.
- State the currently recommended maximum 24-hour dose of acetaminophen and explain drug-drug and alcohol interactions.
- Distinguish potencies of acetaminophen preparations for infants, children, and adults.
- Discuss the FDA rulings on acetaminophen and their recommendations for the future.

## Widespread Use of Acetaminophen

Bob, a 49-year-old construction worker comes to the emergency department with nausea and vomiting that has lasted for two days. He admits to social drinking of 2 beers nightly after work and 4 on weekends for the past 20 years. He states he has been taking 8 tablets of Tylenol daily for the past 2 weeks for pain in his right knee and lower back after a recent fall. He think he may have the flu because he just “doesn’t feel good” and keeps vomiting. Upon physical assessment his skin looks pale yellow and he’s dehydrated. His right knee is swollen and red.

If this patient were your assignment, what labs would you expect to be ordered? What would be your focused physical assessment? What is the primary problem? What is the causative factors? What diagnosis do you suspect?

## What Is acetaminophen?

Acetaminophen is a non-narcotic analgesic and fever reducer. It is available by prescription or over the counter (OTC). 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, which is used to relieve pain or reduce fever (FDA, 2017).

Acetaminophen, also called *paracetamol*, is sold by many names including Tylenol, Panadol, Ofirmev, Acephn, and Mapap. It is used effectively for fever, muscle pain, neck pain, plantar fasciitis, sciatica, and common body aches and pains. It is abbreviated as APAP (for acetyl-para-aminophenol), which is the chemical name, and it is known by 28 brand names in the United States (Mayo, 2017).

It is commonly used **in combination** drugs for pain as a nonnarcotic analgesic and known as Excedrin, Goody's Body Pain, Saleto, Exaprin, Levacet, Painaid, Apadaz, Rhinocaps, and Staflex. Acetaminophen is included in OTC medications for acute cold symptoms, respiratory conditions, and headaches. In addition, it is a component of some narcotic prescriptions.

Acetaminophen can be used as a sole medication or as an active ingredient in many OTC and prescription medicines. Acetaminophen is generally safe at recommended doses, but if taken in larger dosages or frequency, it can cause serious and even fatal liver damage. In fact, acetaminophen poisoning is a leading cause of liver failure in this country (Goldberg, 2017).

### Acetaminophen Tablets (Generic and Trade)



Acetaminophen is available in both generic and trade-named products. Image Source: Google Images.

**Acetaminophen** is very effective in relieving pain and fever, which promotes its popularity. 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 other named 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, the leadership of the National Council for Prescription Drug Programs (NCPDP), the Food and Drug Administration's (FDA) Safe Use Initiative, and a broad group of stakeholders came together in 2011 to form the Acetaminophen Best Practices Task Group, which produced Version 1.0 of a white paper,\* and an update in 2013 (FDA, 2013).

\***White paper:** an authoritative report or guide helping readers to understand an issue, solve a problem, or make a decision.

The recommendations are intended to make it easier for consumers to (1) identify that their prescription pain reliever contains acetaminophen, (2) compare active ingredients on their prescription and OTC labels, and (3) take action to avoid taking two medicines with acetaminophen. One strategy recommended matching the prescription container labeling with the labeling that already exists for OTC medicines that contain acetaminophen, providing consistency in labeling across all acetaminophen-containing medicines.

The **FDA white paper** recommends:

- Complete spelling of acetaminophen and all other active ingredients on the pharmacy labels of all acetaminophen-containing prescription medicine and eliminating the use of abbreviations, acronyms, or other shortened versions for active ingredients
- A standardized liver warning label
- A standardized warning label for drugs that may interact with acetaminophen
- Formatting and wording on pharmacy container labels consistent with plain language and health literacy principles
- A stakeholder call to action: "adopt, implement, adhere, communicate and educate" (FDA, 2013)

Acetaminophen, the active ingredient in Tylenol, is also known as paracetamol and N-acetyl-p-aminophenol (APAP). It has been marketed in the United States as an OTC antipyretic (fever reducing) and analgesic (pain reducing) agent since 1953 (Wikipedia, 2018a). Acetaminophen is widely available in a variety of strengths and formulations for children and adults as a single-ingredient product.

In the United States acetaminophen 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 (Medical Dictionary, 2018). It is available in many forms, including solutions, tablets, suppository, powder, capsule, syrup, suspension, elixir, and effervescent tablets.

Acetaminophen is added to many combination prescription narcotic drugs (Vicodin, Percocet) in order to give more pain relief with a minimized dose of the addictive narcotic component. 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.



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. Image Source: Wikimedia Commons.

## Test Your Knowledge

Acetaminophen is sometimes known as:

- A. APAP or paracetamol.
- B. Indomethacin.
- C. Naproxen.
- D. Ibuprofen.

Acetaminophen is sometimes an ingredient in combination drugs, such as:

- A. Celebrex and Enbrel.
- B. Percocet and Vicodin.
- C. Lisinopril and benazepril.
- D. Viagra and Cialis.

## Apply Your Knowledge

A mother wants to know what over-the-counter medication she can give her 4-year-old for fever. What are the common brand names for acetaminophen?

# Action of Acetaminophen

How does acetaminophen work to reduce fever and pain?

Acetaminophen is used generally for mild to moderate pain relief and fever reduction. It produces analgesic effects by inhibiting cyclooxygenase (COX) enzymes that catalyze the conversion of arachidonic acid, a fatty acid in cell membranes, to prostaglandins that produce pain, inflammation, and fever.

There are two well-studied isoforms, called COX-1 and COX-2. The isoform COX-1 helps with the synthesis of prostaglandins responsible for protection of the stomach lining, while COX-2 mediates the synthesis of prostaglandins responsible for pain and inflammation. Acetaminophen is a relatively greater selective inhibitor of COX-2 enzymes than COX-1 (Drahl, 2014), similar to Celebrex (celecoxib).

Its antipyretic, fever reducing effects are thought to arise from its actions against COX enzymes in the central nervous system, reducing the amount of prostaglandin E2 in the CNS and thereby lowering the temperature set point in the hypothalamus part of the brain. Its anti-inflammatory properties are much weaker than those of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, which inhibit both COX-1 and COX-2 and can irritate the stomach and gastrointestinal (GI) tract.

Acetaminophen is thus less effective or appropriate for chronic inflammatory pain conditions such as rheumatoid arthritis, Lupus or Cohn's; however, it is an excellent choice for osteoarthritis, especially in those patients where aspirin is contraindicated, such as in patients with an aspirin/salicylates allergy or peptic ulcers and other GI sensitivities. Acetaminophen lacks the antithrombotic, blood-thinning properties of aspirin and other NSAIDs, therefore does not inhibit coagulation, an important consideration for pain therapy following minor surgical or dental procedures.



Image Source: Wikimedia Commons.

## Side Effects of Acetaminophen

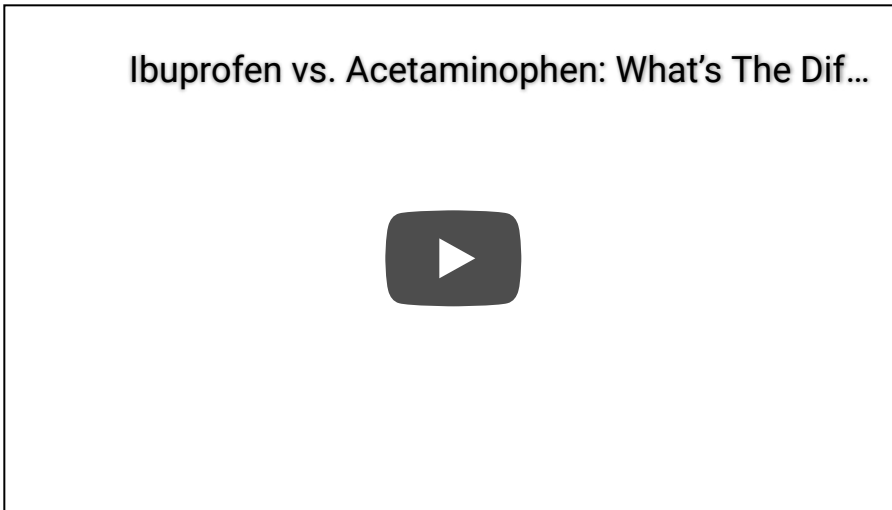
All medications have desired action for which the medication is being taken but also have unwanted side effects, and possibly additional adverse reactions (Drugs.com). The desired effects of acetaminophen are fever-reducing and pain relief, but many people may also experience:

- Dark urine
- Itching
- Jaundice
- Loss of appetite
- Nausea
- Upper stomach pain



## Online Resource

### Ibuprofen vs. Acetaminophen: What's the Difference? (Video 3:27)



<https://www.youtube.com/watch?v=IIPPILw5dtc>

## Mechanisms of Acute-Overdose Liver Failure

Acetaminophen (APAP, paracetamol) has excellent bioavailability when taken orally and is almost completely absorbed by passive transport in the small intestine. Peak plasma concentrations occur at 30 to 60 minutes with a half-life of approximately 2 hours for therapeutic doses as it becomes distributed fairly evenly throughout the body (except for fat tissue).

Acetaminophen is usually metabolized and inactivated in the liver by adding glucuronide or sulfate groups to the molecule for increased solubility and excretion via the kidney (Toyoda et al., 2017) (see figure in next section). A small amount is acted on by the cytochrome P450 enzymes, CYP2E1 and CYP1A2, to generate the very reactive and toxic compound, N-acetyl-p-benzoquinone imine (NAPQI) (Pascal, 2017; Yang, 2017).

Under normal conditions, the liver will detoxify the NAPQI intermediate by adding a glutathione group with the enzyme glutathione-S-transferase (GST), leading to subsequent excretion through the kidney (see figure). A safety warning for people who have chronic and elevated alcohol use, those who take isoniazid for tuberculosis, or those who take St. John's wort, acetaminophen may induce elevated levels of the CYP2E1 enzymes and generate relatively more of the toxic NAPQI compound, depleting the liver's store of protective glutathione antioxidant molecules (Wikipedia, 2018b).

This can result in a higher level of reactive oxygen and eventual necrosis in liver cells (Jaeschke et al., 2012). Likewise, in cases of overdose, intentional or not, the levels of acetaminophen can increase for up to 4 hours, and the NAPQI produced can saturate the GSH detoxification pathway and spill over to cause liver and renal toxicity. The NAPQI compound is toxic because it chemically reacts with other proteins and DNA in the cell, destroying their activity and eventually the mitochondrial function that generates ATP energy (Jaeschke, 2012).

Acute liver toxicity may exhibit clinical symptoms of severe stomach pains, nausea, vomiting, and upper-right-quadrant abdominal sensitivity, leading some to naively take more acetaminophen for pain relief. Liver failure may happen several days after an overdose, and unfortunately the patient may assume the overdose has been resolved, leaving only immediate liver transplant as a saving option.

### Paracetamol/Acetaminophen Metabolism

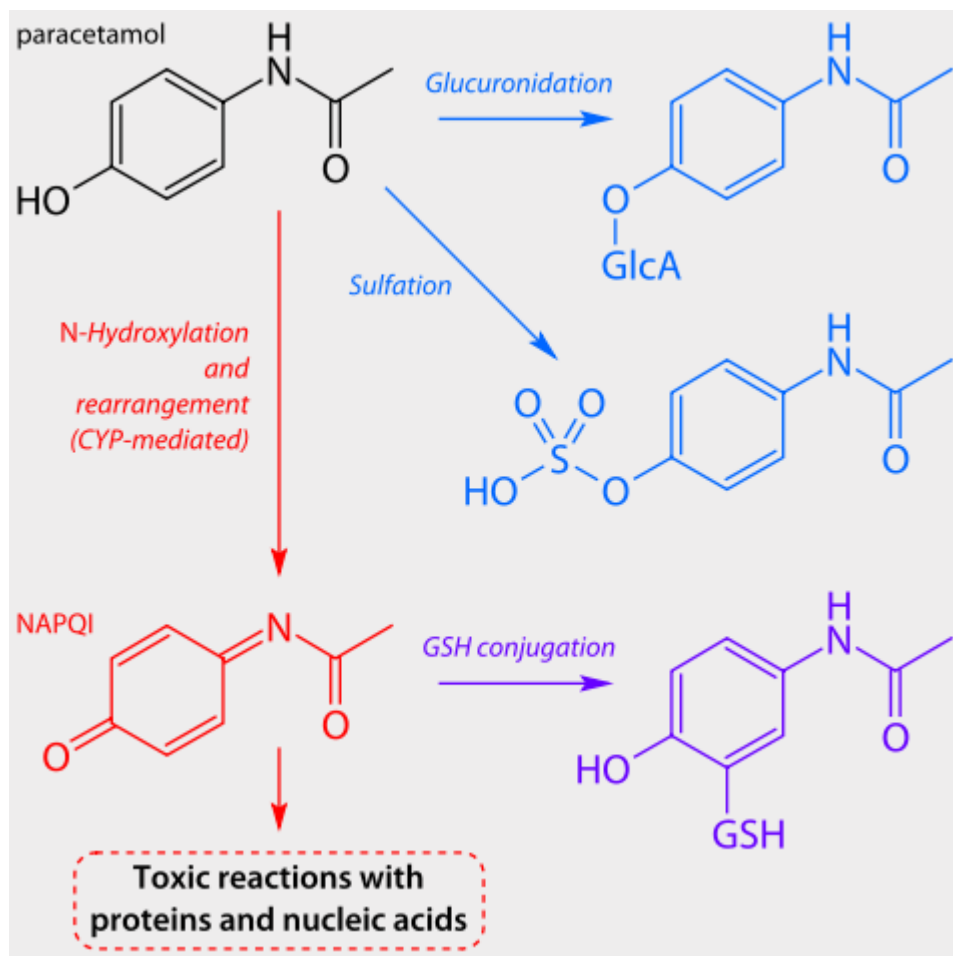


Image Source: Wikimedia Commons.

Our patient Bob has remained in the ED for testing, and results show the following: Vital signs: T, 99.4F; BP, 142/88; R, 20; P, 98.

Physical Exam: sclera mild icterus/yellow

Labs:	Normal
Liver enzymes ALT 558	4–51 IU/L
AST 525	15–45
bilirubin 41	< 17 µmol/L
glucose	50
blood acetaminophen 58 µg/ml	0

The admitting diagnosis is acetaminophen toxicity and Bob is admitted to the hospital. He is given an IV D5W for hydration and given N-acetylcysteine (NAC) as the antidote for acetaminophen overdose.

What put our patient at risk for this? Due to his fall and resultant knee pain he had been self-medicating with a higher than normal dose of acetaminophen. In addition, due to his high alcohol intake, the liver was not able to metabolize the high doses of acetaminophen and created hepatotoxicity.

Patient education and stabilization will be done before he can be discharged. His knee will also require a workup, evaluation, treatment, and appropriate pain management.

## Recommended Dosage

Due to data that revealed unintentional overdoses of acetaminophen, in 2011 the U.S. Food and Drug Administration (FDA) asked drug makers to limit the amount of acetaminophen in prescription combination pain relievers. The goal is to reduce accidental overdoses and the severe liver injury that can follow. This request is hoped to limit the amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients (FDA, 2014).

A Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (eg, swelling of the face, mouth, and throat; difficulty breathing; itching or rash) are being added to the label of all prescription drug products that contain acetaminophen. Manufacturers must also update the labels of all prescription products containing acetaminophen with a Boxed Warning on the risk of severe liver injury if too much acetaminophen is taken or consumed with alcohol (FDA, 2011).

The new dose restriction does not apply to over-the-counter (OTC) pain relievers and cold medicines that contain acetaminophen. Normally, the maximum level allowed for these products is 500 mg, although a few extended-action pain relievers that are taken less frequently can go up to 650 mg (FDA, 2011).

The dosage requirement affects dozens of prescription analgesics that contain both acetaminophen and another ingredient, typically opioids such as codeine, oxycodone, and hydrocodone. Some of these combination products now have as much as 750 mg of acetaminophen per dose.

Patients prescribed analgesics with acetaminophen at doses above 325 mg can safely continue to take them under a physician's supervision. The key to safety is not exceeding the maximum daily dose of 4000 mg, whether it comes in the form of prescription medications, OTC medications, or both (FDA, 2017).

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 (Medical Dictionary, 2018).

#### Did You Know . . .

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 at least some liver damage.

If the patient also consumes alcohol, the risk of damage increases further. 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 (Medical Dictionary, 2018).

## Test Your Knowledge

The current recommended maximum 24-hour dose of Tylenol for adults is:

- A. 1000 mg.
- B. 2400 mg.
- C. 4000 mg.
- D. 6000 mg.

People who consume more than two alcoholic drinks per day should:

- A. Consider rehab before taking any pain medications.
- B. Take no more than 2000 mg per day.
- C. Take only NSAIDs for pain.
- D. Not take acetaminophen at all.

Answers: C,B

Pediatric doses are based on age and weight, usually 10 to 15 mg/kg of body weight for a single dose and no more than five doses in a 24-hour period (Ji et al., 2012). FDA approval for intravenous acetaminophen use in infants and children is also now available (FDA, 2013). 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.

In 2011 an FDA advisory panel announced that pediatric doses of acetaminophen should be labeled “fever reduction only” in children under age 2. The panel found there was too little evidence to label OTC acetaminophen for pain relief in infants under age 2, although doctors often prescribe the drug for this purpose. The advisory panel also re-emphasized that **prescribing acetaminophen for children should be based first on weight and then on age.**

The panel also advised the FDA to require that:

- Bottles of infant acetaminophen carry dosing instructions for ages 6 months to 2 years
- Bottles of liquid acetaminophen be changed to make it harder for kids to open and take an accidental overdose
- Acetaminophen bottles to come with a liquid measuring device clearly marked in milliliters

The FDA announced that an additional less-concentrated form of liquid acetaminophen marketed for “infants” (160 mg/5 mL) would be available at local stores, packaged with an oral syringe rather than a dropper. Until then, liquid acetaminophen marketed for infants had only been available in higher concentrations (80 mg/0.8 mL or 80 mg/1 mL). This change in the concentration affects the amount of liquid given to an infant and should be especially noted if someone is accustomed to using the more concentrated form (Drugs.com, 2018).

The pharmacy industry also announced it would put flow restrictors on liquid acetaminophen bottles to prevent unsupervised children from drinking large amounts of the medication. Companies will provide clearly marked syringes with all products for kids ages 3 and younger and will add clearly marked dosing cups to all products for kids ages 2 to 12.

The maximum amount of acetaminophen in a prescription tablet, capsule, or other dosage unit will be limited to 325 mg. However, the total number of tablets or capsules that may be prescribed and the time intervals at which they may be prescribed will not change as a result of the lower amount of acetaminophen. For example, for a product that previously contained 500 mg of acetaminophen with an opioid and was prescribed as 1 to 2 tablets every 4 to 6 hours, will now contain 325 mg of acetaminophen and the dosing instructions can remain unchanged (FDA, 2017).

It is also advised that if a patient takes the maximum dosage of acetaminophen allowed for two weeks, and the problem isn’t resolved, it is time to review with the physician the cause and better treatment for the pain. Higher doses such as 500 mg/tablet have also not shown to deliver better pain reduction than 325 mg/tablets. Unfortunately, for non-prescription products, the “extra-strength” label that delivers 500 mg/tablet is still available (Consumer Reports, 2014).

### Key Points

- Advise patients not to exceed the acetaminophen maximum total daily dose of 4 grams/day.
- Severe liver injury, including cases of acute liver failure resulting in liver transplant and death, has been reported with the use of acetaminophen.
- Educate patients about the importance of reading all prescription and OTC labels to ensure they are not taking multiple acetaminophen-containing products.
- Advise patients not to drink alcohol while taking acetaminophen-containing medications.
- Rare cases of anaphylaxis and other hypersensitivity reactions have occurred with the use of acetaminophen.
- Advise patients to seek medical help immediately if they have taken more acetaminophen than directed or experience swelling of the face, mouth, and throat, difficulty breathing, itching, and rash.

Source: FDA, 2017.

For a list of marketed acetaminophen-containing prescription products affected by the new dosage unit limits, see Drugs.com (2018).

## Acetaminophen Frequency of Use

Acetaminophen is the most widely used analgesic medication in the United States despite its potential for hepatotoxicity. Over the past few years, the use of combination prescription products has increased dramatically, and is the biggest cause of acetaminophen overdose (Hodgman & Garrard, 2012).

It is estimated 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.

Almost 80,000 people in the United States are treated in Emergency Departments annually due to accidental overdose of acetaminophen (Consumer Reports, 2014). Over 600 OTC and prescription medication products contain acetaminophen.

In the last decade use of these combination prescription products increased 38%. There were more than 182 million prescriptions for combination prescription products 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, 2011).

The U.S. Centers for Disease Control estimate that more than 980 deaths occur each year due to acetaminophen-containing combination drugs and at least 300 people die as a direct result from acetaminophen-only poisoning (Miller, 2013). Since 2006 these death numbers represent more fatalities due to acetaminophen than all other OTC pain relievers and surpassed those who died from intentional overdose to commit suicide.

### Online Resource

#### Acetaminophen Toxicity (Video 6:09)



[https://www.youtube.com/watch?v=xc2QAS\\_kF0A](https://www.youtube.com/watch?v=xc2QAS_kF0A)

### Apply Your Knowledge

What are the risk factors that can augment the potency of acetaminophen and cause liver damage?

## Unintentional Acetaminophen Overdoses



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 (Hodgman & Garrard, 2012). Another study by the Acute Liver Failure Study Group found that nearly 50% of ALF occurrences were due to acetaminophen overdose (NIH, 2013; Thomas, 2018).

### **Test Your Knowledge**

A recent study of acetaminophen-caused liver failure indicated that:

- A. Almost all were accidental.
- B. The number of cases was insignificant.
- C. Almost all were intentional.
- D. Many occurred from combination medicines containing unrecognized acetaminophen dose.

Answer: A

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

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 (Hodgman & Garrard, 2012).

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 may exacerbate 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.

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 (Thomas, 2018).

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 children, elders, and those who use alcohol, have liver disease, suffer from anorexia nervosa, or are fasting, 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 how ethnicity, genetics, nutrition, or other factors play a role in making some individuals more prone to liver injury (Hodgman & Garrard, 2012; Thomas, 2018).

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 (Consumer Reports, 2014).

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 acetaminophen. Not knowing what APAP is, patients may take more than one product containing acetaminophen. For example, a prescription product and an OTC product may contain the same ingredients but be called different things and customers may unintentionally take a harmful overdose.

While many patients recognize that Tylenol contains acetaminophen, fewer know that **Vicodin** (hydrocodone/acetaminophen), **Darvocet** (recalled in 2010) (propoxyphene/napsilate), and **Percocet** (oxycodone/acetaminophen) all contain acetaminophen.

### Label for Combination Drug Vicodin



Note: No warning about overdose of acetaminophen is evident on this Vicodin label.  
Image Source: Wikimedia Commons.

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 and therefore stronger, designed to enable 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 (Budnitz et al., 2011).

STAGE	Time post ingestion	Clinical manifestations
I	0–24 hours	Anorexia, nausea, vomiting
II	24–72 hours	Right upper quadrant abdominal pain, AST/AL elevation
III	72–96 hours	Vomiting, renal failure, pancreatitis, worsening liver enzyme lab values
IV	> 5 days	Multiple organ failure if not treated

Toxic dose: 150 mg/kg (7 g in adult)

The association between acetaminophen and liver injury is not common knowledge. Healthcare professionals are trained in basic pharmacokinetics and have learned that all oral drugs must pass through the liver to be metabolized. Some medications are inherently hepatotoxic and, in overdoses, many drugs can become dangerous to the liver cells.

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 (ex, 500 tablets per bottle). Furthermore, advertisements of OTC products are not required to provide warning information (FDA, 2013).

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.

## Test Your Knowledge

Liquid acetaminophen formulations for infants are:

- A. About the same strength as those intended for older children.
- B. Typically stronger than those intended for older children.
- C. Not as strong as those intended for older children.
- D. Different only from adult formulations.

The onset of liver injury:

- A. Is immediately evident.
- B. Becomes evident within a few hours.
- C. Can take several days, even in severe cases.
- D. Has easily identifiable symptoms.

Answers: B,C

### Prognostic Measures

#### Poor Prognosis

24–48 hours post ingestion:

- Encephalopathy (confusion, somnolence, or coma)
- Coagulopathy (INR >3)
- Elevated bilirubin
- Renal Failure (Creatinine >2.6)
- Metabolic Acidosis
- Hypoglycemia

#### Good Prognosis

- Liver function tests return to baseline with treatment.

Some acetaminophen tests are inaccurate in the presence of bilirubin, N-acetyl cysteine, and ketones. Because the liver also functions to help regulate blood glucose levels, a patient who has a glucose >100 mg/dL will recover better from liver toxicity.

Finding ways to educate consumers about the risk of liver injury from acetaminophen has been difficult. Current labeling on OTC products may be overlooked or not understood, and many patients do not read the patient information provided with dispensed prescriptions. Programs to educate the public about safe use of acetaminophen have been small and have 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.

Many factors contribute to unintentional acetaminophen overdose:

- The recommended daily doses and tablet strengths leave little room for error.
- 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. (Wikipedia, 2018b).

In children, these additional factors contribute to unintentional overdoses:

- Administering the wrong pediatric acetaminophen formulation (eg, substituting the concentrated infant drops for the less concentrated children's suspension)
- Administering the adult dose 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) (Tylenol website, 2018).

## Online Resource

### Acetaminophen Dosage for Children under 2 (Video 3:35)



<https://www.youtube.com/watch?v=KA-Ih9Tnx3w>

## Liver Injury with Acetaminophen Use

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 (Hodgman & Garrard, 2012).

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 generally unintentional rather than suicidal
- Outweighs all other drugs combined (Lee & Larson, 2009)



## Test Your Knowledge

Incidence of acute liver failure (ALF) due to acetaminophen overdose:

- A. Accounts for most liver transplant cases.
- B. Outweighs all other drugs combined.
- C. Is negligible despite ongoing concerns.
- D. Generally results from intentional overdose.

Answer: B

Acetaminophen toxicity is the most common etiology for accidental overdose of OTC medications. 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 (Budnitz et al., 2011).

### Liver Injury, Population Overall

Summarizing data related to acetaminophen-associated overdoses from 2016, there were an estimated:

- 78,000 emergency department visits per year
- 33,000 hospitalizations per year

Acetaminophen overdose and hepatotoxicity is the leading cause of ALF in the United States.

Source: Mosbergen, 2017.

The liver helps break down and remove many chemicals or drugs that enter the body; however, taking too much acetaminophen overloads the liver's ability to process the drug effectively (Jaeschke et al., 2012). 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) (Wikipedia, 2018c).

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 (McGill et al., 2012). 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 (Hodgman & Garrard, 2012).

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, poor nutrition, and/or anorexia nervosa

## 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, by replenishing the stores of glutathione in the liver to detoxify NAPQI. For this reason, it is absolutely necessary that acetaminophen poisoning be recognized, diagnosed, and treated as early as possible (Budnitz et al., 2011). Commercial products (eg, acetdote) are now available as the antidote.

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 such as loss of appetite, nausea, and vomiting, may be mistaken for the flu, or for the very issue that caused the symptoms they are trying to treat with acetaminophen (Hodgman & Garrard, 2012).

## Test Your Knowledge

The early symptoms of liver damage:

- A. Include extreme fatigue.
- B. Are easily detected in severe cases.
- C. Show early as markedly red eyes.
- D. Includes nausea and vomiting.

## Apply Your Knowledge

Q: What are the symptoms of liver toxicity? What expected lab tests should be done and what would you expect to see with hepatotoxicity?

A: 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.

Answer: D

## Treatment

An acetaminophen poisoning diagnosis can be determined by measuring its level in the blood. 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 suspected ingestion, although treatment is begun immediately.

The Rumack-Matthew nomogram (see figure below), first developed in 1976 at the Rocky Mountain Poison Center at Denver and since modified to indicate treatment at a lower threshold, estimates the risk of liver toxicity and injury based on acetaminophen levels in the blood within 4 hours of the known time since ingestion (Rumack et al., 2017).

The level is best determined after at least 4 hours so that any drug ingested has had a chance to be absorbed by the GI tract. This does not mean that protective measures should not be taken prior to 4 hours. A second measurement can confirm the concentration and overdose diagnosis with time.

Protective measures 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, to stay clear of the stomach procedures. Since charcoal will absorb NAC, another stomach lavage may be done prior to oral administration to remove the activated charcoal (Kirchner, 2016).

### Single Acute Acetaminophen Overdose Nomogram

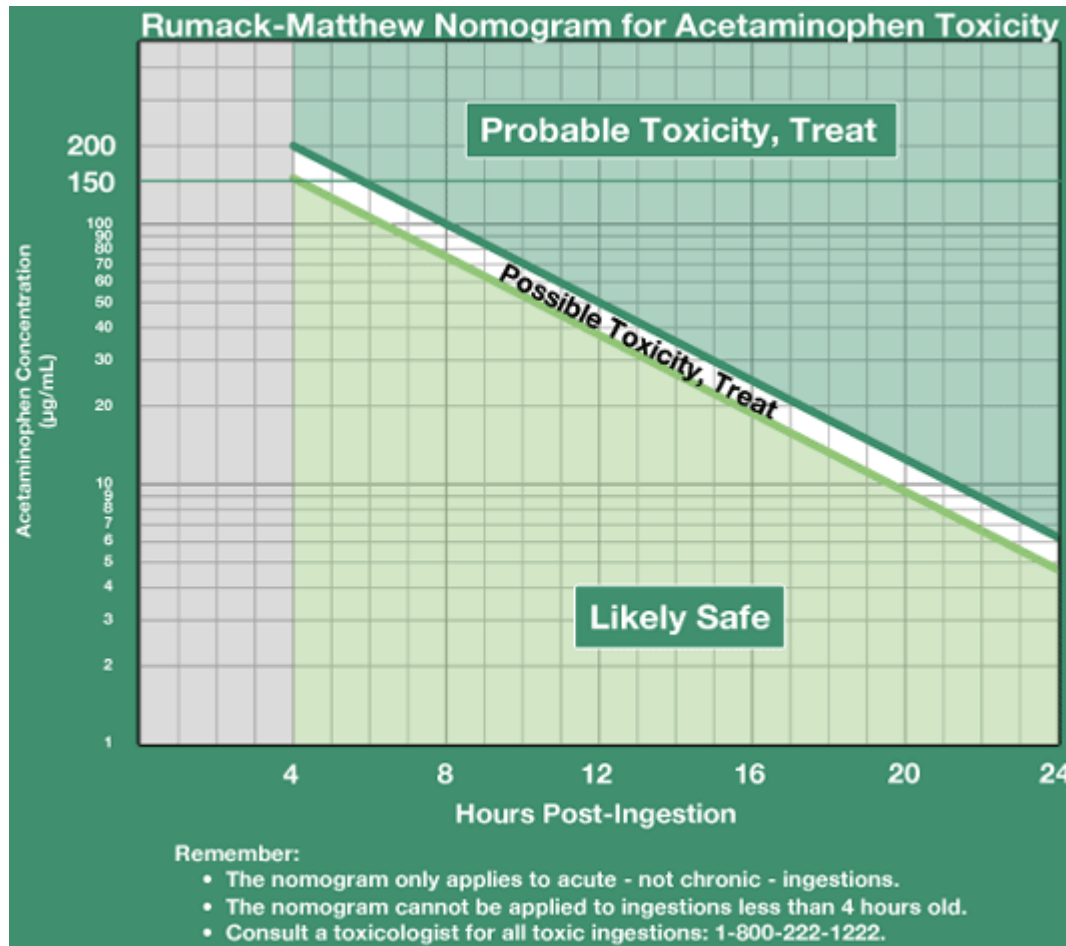


Image Source: Rumack et al., 1981.

Clinical or biochemical evidence of liver toxicity may develop in 1 to 4 days, although it may appear in 12 hours for severe cases. Laboratory studies may show evidence of hepatic necrosis with elevated AST, ALT, bilirubin, and prolonged coagulation times—particularly an elevated prothrombin time (Wikipedia, 2018b).

If the acetaminophen plasma levels are high, the patient may need to be given subsequent maintenance doses of NAC. If given by IV, the loading dose is 150 mg/kg of body weight in 15 to 30 minutes; the maintenance doses are 50 mg/kg of body weight for 4 hours, and 100 mg/kg every 4 hours for the following 16 hours, with the final dose of 10 mg/kg to be repeated three times until the liver enzyme lab levels have normalized (Mahmoudi, 2014).

Anytime an overdose of any medication occurs in a hospital setting, an incident report is needed to evaluate the cause and possible prevention strategies. In addition to the clerical responsibilities of drug overdose, the emotional effects can be devastating due to guilt, especially when innocent children are involved. Patient and caregiver education is essential to help identify the causative factors, which may lead to prevention guidelines and corrective instruction. As always, an ounce of prevention in education, is better than a pound of cure, especially when it comes to accidental drug overdose.

### Test Your Knowledge

To respond to an overdose of acetaminophen:

- A. Administer fluids stat 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.

### Apply Your Knowledge

How is NAC given for an acetaminophen overdose? Does your clinic/hospital have access to it? Is it on your unit? What is the procedure for administration?

### Online Resource

**N-acetyl Cysteine Uses, Antidote Effects for Paracetamol, Mechanism, Indications and ADRS (Video 1:42)**

N-acetyl cysteine uses, antidote effects for p...



<https://www.youtube.com/watch?v=22PUYv9JAwk>

Answer: C

# The Safe Use of Acetaminophen

The FDA gives the following advice to **consumers** on 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.

## Test Your Knowledge

Concerning acetaminophen, a child should be given:

- A. An increased dose if the previous dose was ineffective.
- B. Only one medication containing acetaminophen at a time.
- C. A dose determined solely by the age of the child.
- D. A little extra to make up for a missed dose.

Answer: B

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 national poison control center phone number is available 24 hours a day, 7 days a week, and 35 days a year.

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.

## **Use of Acetaminophen in Elders and Children**

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 (Farrell et al., 2018).

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.

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

Older adults have narrow therapeutic windows (due to decreased metabolism and liver drug clearance levels), and require close monitoring, especially when on multiple medications and with potentially compromised liver and kidney function. 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 (Farrellet al., 2018).

The American Geriatrics Society (2009) states that the maximum 24-hour dose of acetaminophen in most older persons 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.



## Test Your Knowledge

Older adults using acetaminophen need special attention because:

- A. They came of age during a time of widespread recreational drug use.
- B. Poor vision or cognition may cause inability to follow medication regimens.
- C. They are not accustomed to over-the-counter medications.
- D. Dosages need to be higher because of common aches and pains.

## Online Resource

### **An NP's Role in Supporting Appropriate NSAID and Acetaminophen Dosages (Video 4:55)**



<https://www.youtube.com/watch?v=0zEERwncVWY>

Answer: B

## Children

Acetaminophen is a common treatment for pain and fever in children and is available OTC primarily in liquid form. Parents need to use caution when administering liquid acetaminophen. Acetaminophen comes in two strengths, a suspension to be used for older children and infants, 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 (Brass, 2018).

The manufacturers 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 (Brass, 2018; Buck, 2011).

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.

### **Acetaminophen Dosage for Infants and Children**

Another concentration (160 mg/5 mL) of liquid acetaminophen marketed for "infants" is now available in stores. This product is less concentrated than other liquid acetaminophen products marketed for children. The other products currently available are in 80 mg/0.8 mL and 80 mg/1 mL concentrations.

The 160 mg/5 mL acetaminophen marketed for infants may be packaged with an oral syringe instead of a dropper. It is important to use only the dosing device provided with the product. **Do not mix and match dosing devices.**

The concentration of liquid acetaminophen should be included on a prescription because multiple products with different concentrations are available.

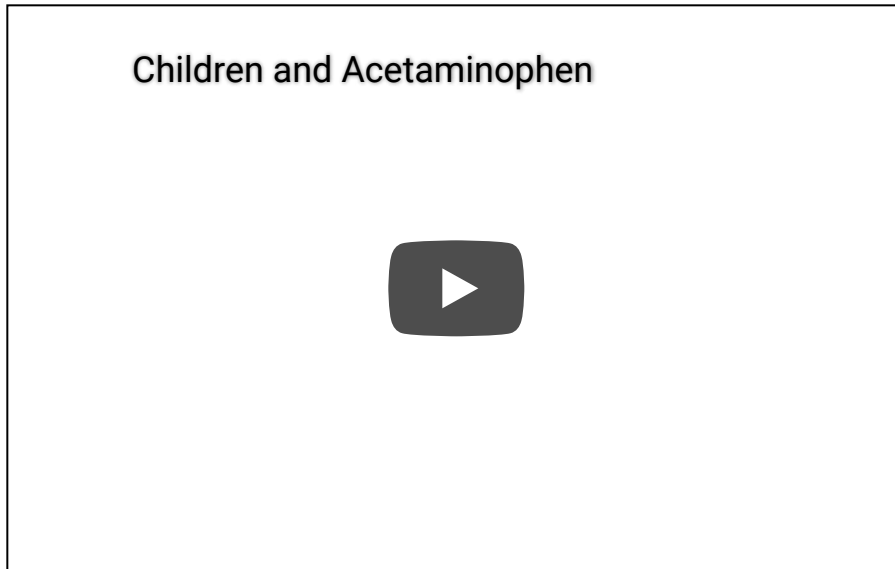
Healthcare professionals should use their clinical judgment to recommend the most appropriate liquid acetaminophen product for children under the age of 12, and they should counsel caregivers on product differences.

Healthcare professionals should report adverse events or medication errors involving OTC infant acetaminophen products to the FDA MedWatch program.

Source: Brass, 2018.

## Online Resource

### Children and Acetaminophen (Video 1:58)



<https://www.youtube.com/watch?v=QDfgpMri0Y8>

## 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, and ethanol, isoniazid for tuberculosis, and St. John's wort all induce higher levels of the CYP2E1 enzyme that generates the toxic NAPQI metabolite and depletes the glutathione antioxidant needed to clear it.

The increased amount of the toxic metabolite NAPQI produced may cause liver cell stress or death (Hodgman & Garrard, 2012). Many of the drug interactions listed below result from shared metabolism and competition for the same liver enzymes, or an induced or reduced level of enzyme that exacerbates safe co-administration.

## 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 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 (Hughes et al., 2011).

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 (Hughes et al., 2011).

As alluded to earlier, 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 (NIH, 2013).

#### Did You Know . . .

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 (Medicine Net, 2018).

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 from acetaminophen and can therefore increase liver damage (Medicine Net, 2018).

## Test Your Knowledge

People who take warfarin to prevent blood clots:

- A. May be at risk for bleeding if they also take acetaminophen.
- B. Can also take acetaminophen so long as they don't exceed the 24-hour maximum.
- C. Will benefit by the addition of acetaminophen and have even fewer blood clots.
- D. May offset the benefits of the warfarin if they take acetaminophen.

## Apply Your Knowledge

What patient education is needed for patients who are taking Coumadin or isoniazid for OTC pain relief? What symptoms would you teach them to be aware of?

Answer: A

# FDA Rulings on Acetaminophen Labeling

## OTC Labeling

In 2009 the FDA issued a rule that strengthens the labeling for OTC products containing acetaminophen. The following box lists some of the labeling requirements, 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, 2013).

## **Labeling Requirements for OTC Products Containing Acetaminophen**

- 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, 2013.

## Test Your Knowledge

FDA ruling on labeling of acetaminophen:

- A. Applies only to combination drugs.
- B. Includes alcohol and liver warnings.
- C. Mandates a 5-year period for implementation of changes.
- D. Found that no changes were necessary.

## Apply Your Knowledge

Next time you are in the grocery store, check out the pharmacy area and explore how many different products have acetaminophen and notice how they are labeled. Is it confusing? What could be done to make the labeling easier to understand for the lay public?

Answer: B

## Prescription Labeling

## **Recommendations for Labeling on Prescriptions Containing Acetaminophen**

The following is the FDA's Summary of Recommendations to Improve Prescription Container Labeling for Medicines Containing Acetaminophen.

1. Complete spelling of active ingredients in acetaminophen-containing prescription medicines.
  - Completely spell all active ingredients in acetaminophen-containing medicine on the prescription container label. No acronyms, abbreviations, or truncations for acetaminophen or any other active ingredients should be used.
  - When a brand or branded generic medicine is dispensed, completely spell all active ingredients in addition to the branded name.
2. Acetaminophen concomitant use and liver warning label
  - Adopt one standard concomitant use and liver warning label in alignment with the OTC acetaminophen warnings on Drug Facts labels. This will make the messaging consistent and strengthen and reinforce the messaging for patients across all acetaminophen-containing medicines.
  - Adopt a standard hierarchy for the key messages on the warning label for these labels.
  - Delete all warning labels containing similar key messages from warning label data files to prevent duplication of key messages on prescription labels.
3. Prioritization of warning label printing
  - Prioritize the standard warning label to print within the top 3 warning labels to increase the probability the label will print and be applied to prescription containers.
4. Icons on pharmacy warning labels
  - Icons can be used on warning labels if testing has proven the icons improve consumer and patient understanding beyond simple explicit text alone.



- Manufacturers of acetaminophen-containing medicines, working through Consumer Healthcare Products Association (CHPA) and in collaboration with academia, are currently conducting research to explore the effectiveness of an acetaminophen-ingredient icon for cross-industry inclusion on both OTC (Drug Facts label) and prescription container labels.

#### 5. Patient-centered pharmacy warning labels

- Employ general health literacy and plain language principles on the warning label to promote patient readability and understanding.
- Patient-centered labels should reflect strategies (simple, clear language; font type and size) that promote optimal readability of critical information, consistent with recommendations by health literacy experts, plain language experts, and other organizations that have addressed patient-centered approaches to labeling in order to maximize readability and patient comprehension.

The US Food and Drug Administration (FDA) has added all acetaminophen-containing products to its quarterly list of products to monitor because of possible signals of serious risks or new safety information. The agency receives reports of possible adverse events for these products in the FDA Adverse Event Reporting System (FAERS) database annually.

Making the watch list does not mean that the FDA has determined that the drug poses the specific health risk reported through FAERS. What it does mean is that the FDA will investigate whether there is a causal link.

All products containing acetaminophen appear on the latest watch list because of reports of severe skin reactions. Dermatologic disorders are known adverse reactions associated with these analgesics. The FDA is not suggesting that clinicians should stop prescribing it or that patients should stop taking it, but rather to be aware of its high risk for adverse reactions (PEI, 2018).

## Test Your Knowledge

The current FDA ruling on labeling acetaminophen included all but one of the following:

- A. Complete spelling of all active ingredients.
- B. Icons on pharmacy warning labels.
- C. Patient-centered labels.
- D. A warning about the potential for kidney disease.

Answer: D

## Conclusion

Acetaminophen is one of the most commonly used drugs in the United States to reduce pain and fever. But, despite its popularity, efficacy, and general safety when used according to dosing instructions, acetaminophen is the leading cause of acute liver failure in this country. 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.

In particular, there has been a disproportionate increase in liver injury in recent years as a result of misuse of acetaminophen-containing prescription medicines. Liver abnormalities caused by acetaminophen toxicity can range from abnormalities in liver function blood tests to acute liver failure and death.

Due to numerous reports of accidental overdose, the pharmacy industry's voluntary responses to the FDA's concerns have provided significant improvement to prescription container labels for acetaminophen-containing medicines.

However, continuing these efforts to implement the NCPDP recommendations needs to remain a priority for all stakeholders identified in the White Paper. Consistency across OTC and prescription container labels is a critical first step to enable consumers and patients to identify and compare ingredients and take steps to improve their appropriate and safe use of acetaminophen.

## Resources and References

### Resources

## **Acetaminophen Safe Use Toolkit**

<http://www.bemedwise.org/acetaminophen/teen-influencers>

## **American Association of Poison Control Centers**

[www.aapcc.org](http://www.aapcc.org)

## **Consumer Med Safety**

<http://www.consumermedsafety.org/medication-safety-articles/item/612-available-resource-for-safe-acetaminophen-use>

## **IV Acetadote Dosage Calculator**

<http://acetadote.com/dosecalc.php>

## **NCPIE Be Medwise** (free printable resources)

<http://www.bemedwise.org/health-education-resources/medication-information-library>

## **Patient Education Institute. Website XPlain**

<http://www.patient-education.com/englisha/topic/ie-acetaminophen-safety>

## **Tylenol for Healthcare Professionals: Safety and Patient Education**

[https://www.tylenol.com/products/tylenol-rapid-release-gels?](https://www.tylenol.com/products/tylenol-rapid-release-gels?utm_source=bing&utm_medium=cpc&utm_campaign=BI-USA-ENG-PS-Tylenol%20EST-BP-BM-RN-Conditions&utm_content=Fever&utm_term=+tylenol%20for%20fever&gclid=CPH73MH39NoCFaePxQIdwUkJTw)

[utm\\_source=bing&utm\\_medium=cpc&utm\\_campaign=BI-USA-ENG-PS-Tylenol%20EST-BP-BM-RN-](https://www.tylenol.com/products/tylenol-rapid-release-gels?utm_source=bing&utm_medium=cpc&utm_campaign=BI-USA-ENG-PS-Tylenol%20EST-BP-BM-RN-Conditions&utm_content=Fever&utm_term=+tylenol%20for%20fever&gclid=CPH73MH39NoCFaePxQIdwUkJTw)

[Conditions&utm\\_content=Fever&utm\\_term=+tylenol%20for%20fever&gclid=CPH73MH39NoCFaePxQIdwUkJTw](https://www.tylenol.com/products/tylenol-rapid-release-gels?utm_source=bing&utm_medium=cpc&utm_campaign=BI-USA-ENG-PS-Tylenol%20EST-BP-BM-RN-Conditions&utm_content=Fever&utm_term=+tylenol%20for%20fever&gclid=CPH73MH39NoCFaePxQIdwUkJTw)

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# Post Test: Acetaminophen (239)

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

1. Acetaminophen is sometimes known as:
  - a. APAP or paracetamol.
  - b. Indomethacin.
  - c. Naproxen.
  - d. Ibuprofen.
2. Acetaminophen is sometimes an ingredient in combination drugs, such as:
  - a. Celebrex and Enbrel.
  - b. Percocet and Vicodin.
  - c. Lisinopril and benazepril.
  - d. Viagra and Cialis.
3. The current recommended maximum 24-hour dose of Tylenol for adults is:
  - a. 1000 mg.
  - b. 2400 mg.
  - c. 4000 mg.
  - d. 6000 mg.
4. People who consume more than two alcoholic drinks per day should:
  - a. Consider rehab before taking any pain medications.
  - b. Take no more than 2000 mg per day.
  - c. Take only NSAIDs for pain.
  - d. Not take acetaminophen at all.
5. A recent study of acetaminophen-caused liver failure indicated that:
  - a. Almost all were accidental.
  - b. The number of cases was insignificant.
  - c. Almost all were intentional.
  - d. Many occurred from combination medicines containing unrecognized acetaminophen dose.

6. Liquid acetaminophen formulations for infants are:

- a. About the same strength as those intended for older children.
- b. Typically stronger than 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. Can take several days, even in severe cases.
- d. Has easily identifiable symptoms.

8. Incidence of acute liver failure (ALF) due to acetaminophen overdose:

- a. Accounts for most liver transplant cases.
- b. Outweighs all other drugs combined.
- c. Is negligible despite ongoing concerns.
- d. Generally results from intentional overdose.

9. The early symptoms of liver damage:

- a. Include extreme fatigue.
- b. Are easily detected in severe cases.
- c. Show early as markedly red eyes.
- d. Include nausea and vomiting.

10. To respond to an overdose of acetaminophen:

- a. Administer fluids stat 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. Concerning acetaminophen, a child should be given:

- a. An increased dose if the previous dose was ineffective.
- b. Only one medication containing acetaminophen at a time.



- c. A dose determined solely by the age of the child.
- d. A little extra to make up for a missed dose.

12. Older adults using acetaminophen need special attention because:

- a. They came of age during a time of widespread recreational drug use.
- b. Poor vision or cognition may cause inability to follow medication regimens.
- c. They are not accustomed to over-the-counter 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 risk for bleeding if they also take acetaminophen.
- b. Can also take acetaminophen so long as they don't exceed the 24-hour maximum.
- c. Will benefit by the addition of acetaminophen and have even fewer blood clots.
- d. May offset the benefits of the warfarin if they take acetaminophen.

14. FDA ruling on labeling of acetaminophen:

- a. Applies only to combination drugs.
- b. Includes alcohol and liver warnings.
- c. Mandates a 5-year period for implementation of changes.
- d. Found that no changes were necessary.

15. The current FDA ruling on labeling acetaminophen included all but one of the following:

- a. Complete spelling of all active ingredients.
- b. Icons on pharmacy warning labels.
- c. Patient-centered labels.
- d. A warning about the potential for kidney disease.

# Answer Sheet

## Acetaminophen (239)

Name (Please print your name): \_\_\_\_\_

Date: \_\_\_\_\_

Passing score is 80%

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_
6. \_\_\_\_\_
7. \_\_\_\_\_
8. \_\_\_\_\_
9. \_\_\_\_\_
10. \_\_\_\_\_
11. \_\_\_\_\_
12. \_\_\_\_\_
13. \_\_\_\_\_
14. \_\_\_\_\_
15. \_\_\_\_\_

# Course Eval: Acetaminophen (239)

Please use this scale for your course evaluation. Items with asterisks \* are required.

- 5 = Strongly agree
- 4 = Agree
- 3 = Neutral
- 2 = Disagree
- 1 = Strongly disagree

\* Upon completion of the course, I was able to:

a. Explain the widespread use of acetaminophen both as an over-the-counter drug (OTC) and by prescription in combination with other drugs.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

b. Discuss self-dosing of acetaminophen as an OTC drug and the hazard of unintentional overdose.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

c. Describe the relationship of acetaminophen to acute liver failure.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

d. State the currently recommended maximum 24-hour dose of acetaminophen and explain drug-drug and alcohol interactions.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

e. Distinguish potencies of acetaminophen preparations for infants, children, and adults.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

f. Discuss the FDA rulings on acetaminophen and their recommendations for the future.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

\* The author(s) are knowledgeable about the subject matter.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

\* The author(s) cited evidence that supported the material presented.

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

\* This course contained no discriminatory or prejudicial language.

☐ Yes ☐ No

\* The course was free of commercial bias and product promotion.

☐ Yes ☐ No

\* As a result of what you have learned, do you intend to make any changes in your practice?

☐ Yes ☐ No

If you answered Yes above, what changes do you intend to make? If you answered No, please explain why.

\* Do you intend to return to ATrain for your ongoing CE needs?

- ☐ Yes, within the next 30 days.
- ☐ Yes, during my next renewal cycle.
- ☐ Maybe, not sure.
- ☐ No, I only needed this one course.

\* Would you recommend ATrain Education to a friend, co-worker, or colleague?

- ☐ Yes, definitely.
- ☐ Possibly.
- ☐ No, not at this time.

\* What is your overall satisfaction with this learning activity?

☐ 5 ☐ 4 ☐ 3 ☐ 2 ☐ 1

\* Navigating the ATrain Education website was:

- ☐ Easy.
- ☐ Somewhat easy.
- ☐ Not at all easy.

\* How long did it take you to complete this course, posttest, and course evaluation?

- ☐ 60 minutes (or more) per contact hour
- ☐ 50-59 minutes per contact hour
- ☐ 40-49 minutes per contact hour
- ☐ 30-39 minutes per contact hour
- ☐ Less than 30 minutes per contact hour

I heard about ATrain Education from:

- ☐ Government or Department of Health website.
- ☐ State board or professional association.
- ☐ Searching the Internet.
- ☐ A friend.
- ☐ An advertisement.
- ☐ I am a returning customer.
- ☐ My employer.
- ☐ Other
- ☐ Social Media (FB, Twitter, LinkedIn, etc)

Please let us know your age group to help us meet your professional needs.

- ☐ 18 to 30
- ☐ 31 to 45
- ☐ 46+

I completed this course on:

- ☐ My own or a friend's computer.
- ☐ A computer at work.
- ☐ A library computer.
- ☐ A tablet.
- ☐ A cellphone.
- ☐ A paper copy of the course.

Please enter your comments or suggestions here: \_\_\_\_\_

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# Registration Form: Acetaminophen (239)

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

\* Name: \_\_\_\_\_

\* Email: \_\_\_\_\_

\* Address: \_\_\_\_\_

\* City: \_\_\_\_\_ \* State: \_\_\_\_\_ \* Zip: \_\_\_\_\_

\* Country: \_\_\_\_\_

\* Phone: \_\_\_\_\_

\* Professional Credentials/Designations:

\_\_\_\_\_

\* License Number and State: \_\_\_\_\_

\* Please email my certificate:

☐ Yes ☐ No

(If you request an email certificate we will not send a copy of the 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**.

2 contact hours: \$19

## Credit card information

\* Name: \_\_\_\_\_

Address (if different from above): \_\_\_\_\_

\* City: \_\_\_\_\_ \* State: \_\_\_\_\_ \* Zip: \_\_\_\_\_

\* Card type:

☐ Visa ☐ Master Card ☐ American Express ☐ Discover

\* Card number: \_\_\_\_\_

\* CVS#: \_\_\_\_\_

\* Expiration date: \_\_\_\_\_