ACETAMINOPHEN BASICS:

- Acetaminophen is one of the most widely used drugs, and a constituent in over 400 different OTC and prescription meds
  - More than 4 billion doses sold each year in Canada
- Provides temporary mild analgesia – headache, toothache, muscle pain, cold/flu symptoms, menstrual symptoms
- Has antipyretic effect but little anti-inflammatory activity (unlike NSAIDs)
- Available in tablets, liquid, gel cap, powder, injectable, suppository
  - Most commonly available as tablets/capsules for oral dosing containing 325 mg or 500 mg of acetaminophen
  - For pediatric use, suspension containing 80 or 160 mg/5mL is available, along with chewable tablets
- Can be combined with other analgesics (ex// codeine) – less common now
- Acetaminophen generally considered safe at therapeutic doses
  - Current recommended dose for adults is 650 – 1000 mg every 4 hours, to a maximum of 4,000 mg per day
  - In US, the maximum dose has been reduced to 3000 mg per day and only 325 mg tablets are available
- Acetaminophen overdose (intentional or accidental) is the most common cause of acute liver failure in many countries

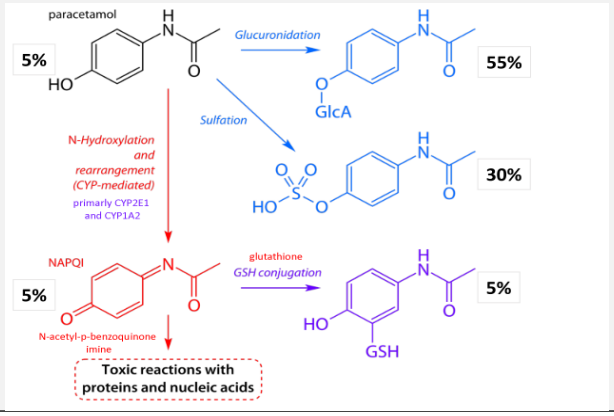
ACETAMINOPHEN PHARMACOLOGY:

- Mechanism of action still not fully understood
- Has some capacity for inhibition of cyclooxygenase function probably in the CNS, but little peripherally – hence no significant GI or CV side effects
- Also believed to work indirectly through a metabolite (AM404) which modules the endogenous cannabinoid system in the CNS, and interacts with TRPV1 channels
- Acetaminophen metabolite NAPQI activates TRPA1, a sensor of noxious stimuli, suggesting another mechanism for its analgesic effect

ACETAMINOPHEN PHARMACOKINETICS:

- Rapidly absorbed from the GI tract
- Oral bioavailability up to 90%
- Volume of distribution approx. 0.9 L/kg
- Half life approx. 2.5 hours
- Clearance 20 L/hrs
- Plasma protein binding < 20%
- Up to 95% of a therapeutic dose is recovered in urine in 24h
  - No more than 5% as unchanged drug
- Extensively metabolized to sulfate, glucuronide conjugates
- Oxidative metabolism results in highly toxic metabolite that is normally detoxified by conjugation with glutathione

ACETAMINOPHEN METABOLISM:



ACETAMINOPHEN TOXICITY-RELATED ER CASES IN US (2006-2010):

- 625 million ER visits → 412,000 acetaminophen related → 45% inpatient
- 66% of cases female, average age 29
- In 12-20 age group: 75% female, 71% self-harm

ACETAMINOPHEN TOXICITY:

- In therapeutic doses, acetaminophen is excreted in urine as sulfate and glucuronide conjugates
  - NAPQI is the toxic metabolite of acetaminophen, mainly through formation of protein adducts
  - In therapeutic doses, formation of NAPQI is minimal, and whatever is produced is conjugated with glutathione and excreted in bile
- In overdose (at least >7.5 g, usually more) sulfation (first) and glucuronidation pathways are saturated, so more is converted to NAPQI
  - Excess NAPQI depletes glutathione stores, leading to reaction of NAPQI with sulfydryl groups on proteins → protein adduct formation
  - Formation of mitochondrial protein adducts is believed to be the most important event for the development of toxicity
- Liver damage by acetaminophen is mediated by the formation of adducts with proteins of the mitochondrial electron transport chain, resulting in:
  - Inhibition of mitochondrial respiration
  - Mitochondrial oxidative stress
  - Formation of superoxide (O_2^-) and peroxynitrite ($ONOO^-$)
  - Collapse of the membrane potential
  - Cellular necrosis

CLINICAL STAGES OF ACETAMINOPHEN TOXICITY:

Stage	Time	Liver Effects	S/S
1	0-24 hr	Subclinical	• None • General malaise • Abdominal pain • Normal LFTs possible
2	24-72 hr	Hepatotoxicity	• Abd. pain (right upper quadrant) • Slightly abnormal LFTs (AST, ALT, possibly bilirubin ↑) • Mild coagulopathy

3	72-96 hr	Hepatic failure with encephalo-pathy	• Very abnormal LFTs
			• Liver failure signs:
			  ○ Jaundice
			  ○ Vomiting
			  ○ Diarrhea
			  ○ Encephalopathy
			  ○ Acidosis
			  ○ Acute renal failure possible

4	>96 hr	Survival or death	• Full restoration of normal organ fxn **OR** • Multi-organ system failure and death

ACETAMINOPHEN OVERDOSE EPIDEMIOLOGY:

OVERVIEW	• Approx. 4500 hospitalizations in Canada annually for acetaminophen overdose
	  ○ Up to 20% of these are unintentional
	• Intentional overdose often spur of the moment
	  ○ Involves dug already in possession	

MORE COMMON IN	• Young people • Females • Alcohol abusers	• Indigenous people • People receiving social assistance
SYMPTOMS	• Depends on dose ○ May be none • Nausea/vomiting • Abdominal pain	• Abnormal liver fxn • Acute liver failure • Death
HIGHER RISK OF LIVER DAMAGE:	• Have existing liver disease (ex// hepatitis) • Drink heavily on a regular basis • Use acetaminophen chronically even at recommended dose • Are malnourished	
OUTCOMES	• Acute liver failure can lead to hepatic encephalopathy which carries approx. 35% mortality rate	
FACTORS PREDICTING OUTCOME	• Late presentation (>24h post ingestion) • Acidosis (pH < 7.3) • Coagulopathy (INR > 3) • Renal failure • Hepatic encephalopathy • Age > 45 • (Unintentional overdose)	

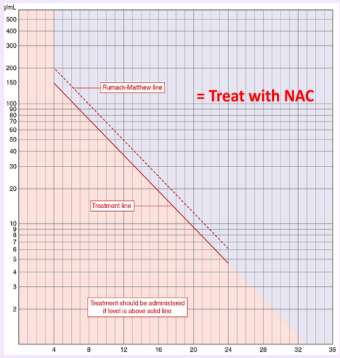
TREATMENT FOR ACETAMINOPHEN OVERDOSE:

- Preventing absorption of ingested acetaminophen using activated charcoal is sometimes used if exposure was relatively recent
- The main txt for overdose is based on the replenishment of depleted glutathione by administration (generally IV) of N-acetylcysteine (NAC)
- Success of treatment depends on the dose of acetaminophen taken, the length of time before treatment, and the NAC protocol
- Treatment monograms are used to guide decision making

N-ACETYLCYSTEINE:

- First licensed in 1968
- Prodrug for L-cysteine, component of glutathione
- Replenishes glutathione store
- Increases sulfation of acetaminophen
- Antioxidant, anti-inflammatory
- May have some use in non-acetaminophen acute liver failure
- Positive inotrope

N-ACETYLCYSTEINE TREATMENT NOMOGRAM: Rumack-Matthew nomogram



- Predicts hepatotoxicity at a given point in time
- Used to guide txt with NAC after a single acute ingestion
- Not used for chronic ingestion
- Dotted line is original proposed by Rumack & Matthew in 1975
- Treatment line (solid) introduced later to take into account potential errors in plasma acetaminophen assays and/or estimated post-ingestion time

PROBLEMS WITH ACETAMINOPHEN:

- Readily available in large quantity (in North America at least)
- Multiple OTC products containing acetaminophen
  - Problematic in elderly
  - Unintentional overdose easily occurs
- Intentional overdose
- Debate over "safe" dose
- Interactions with alcohol
  - Heavy drinkers may be more susceptible to toxicity
  - Acute alcohol exposure may be protective
- Large age-related differences in acetaminophen pharmacokinetics

BLISTER PACKING AND REDUCED PACK SIZE IN UK:

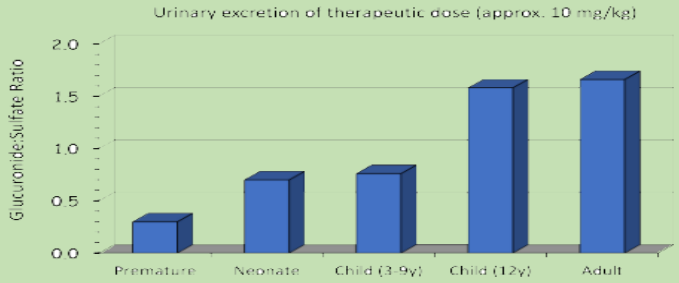
- Since September 1998, acetaminophen is only available in blister packs:
  - 16 tablets (supermarkets and other outlets); max purchase 2 packs
  - 32 tablets (pharmacies)
- A prescription is required for > 100 tablets

ACETAMINOPHEN AND ALCOHOL:

- Interaction b/w acetaminophen toxicity & alcohol is complex/controversial
- Acute alcohol ingestion is not a risk factor for toxicity
  - May in fact be protective due to competition for CYP2E1
- Chronic alcohol consumption may increase risk of toxicity
  - Alcohol enhances CYP2E1
  - Impairment of glutathione synthesis
  - Underlying liver disease
  - Malnourishment
- Absence of clinical trial evidence for the effect of alcohol

AGE-RELATED DIFFERENCES IN ACETAMINOPHEN METABOLISM:

- Metabolic routes of acetaminophen metabolism are distinctly different in children and adults
- In premature and term infants, and in children up to 12 years old sulfation predominates over glucuronidation
- CYP2E1 is not present in early neonates but develops to adult levels by approx. 10 years of age
- Glutathione S-transferases tend to be expressed at higher levels in the fetus and neonate than in adults
- Little difference in overall rate of acetaminophen elimination



UNINTENTIONAL OVERDOSE CASES HAVE POORER OUTCOME:

- Large study in Scottish Liver Transplant Unit
  - 663 cases of acetaminophen overdose
  - 110 cases of unintentional overdose
- Unintentional overdose = older, alcohol abuse
  - Associated with opiate/acetaminophen combinations
  - Lower acetaminophen and ALT blood levels on admission
  - Increased mortality compared to intentional overdose
  - Unintentional overdose independently predictive of death or liver transplantation (OR = 1.91)

ACETAMINOPHEN TOXICITY AT "SAFE DOSE":

- A number of studies indicate that acetaminophen may induce hepatotoxicity when taken at the recommended dose
- Increased levels of abnormal liver function markers detected after taking 4g acetaminophen daily for 14 days
  - In one study, 40% of participants had ALT levels > 3x ULN
- LFTs tend to return to normal after discontinuing drug

SHOULD ACETAMINOPHEN REMAIN OTC?

FDA Interventions on Acetaminophen

1998
- An updated warning label concerning acetaminophen use and alcohol consumption was issued to limit the possibility of hepatotoxicity.[9,11,13]

2002
- An additional recommendation to place more comprehensive hepatotoxicity warnings on all acetaminophen products was issued.[9,11,13]

2009
- Acetaminophen labelling was changed to highlight acetaminophen within combination products. Further, warnings were placed on all prescription acetaminophen products indicating the risk of liver injury and the possibility of a rare but serious hypersensitivity reaction when acetaminophen is used.[9,10]
- The amount of acetaminophen in children's liquid medications was standardised by manufactures to 160 mg/5 mL, and concentrated infant drops were discontinued.[12]

2013
- Another warning was issued that highlighted the association of acetaminophen with fatal skin reactions.[9,10] In 2014, in response to the increasing number of cases of acetaminophen toxicity, the U.S. Food and Drug Administration limited the amount of acetaminophen found in prescription combination products to 325 mg per tablet or capsule.[1]