



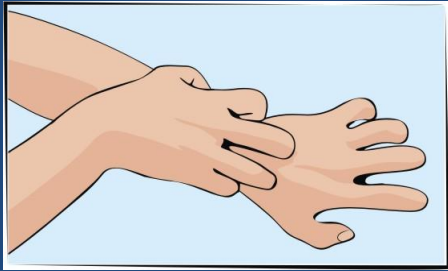
Managing Pruritus and Sleep Disorders Related to Liver Disease

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Objectives

- Understand the mechanisms for pruritus
- Review the treatments for pruritus in liver disease
- Understand liver issues that might relate to poor sleep



Pruritus



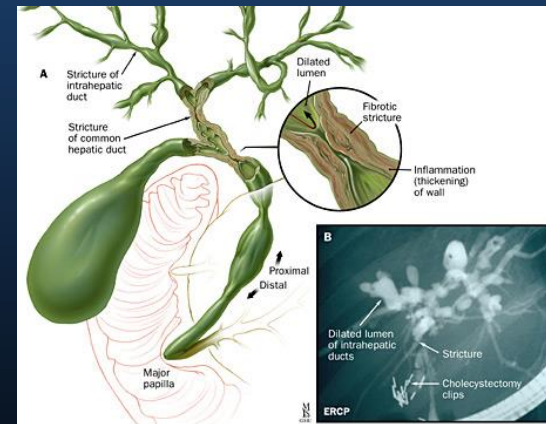
- Severe itching of the skin
- *“In both [types of icterus]...the whole body is itchy...the bilious particles become prickly.”*

-Arataeus, the Cappadocian (circa 160 A.D.)

- Common symptom of liver disease with poor bile flow (*cholestasis*)

- *Cholestatic liver diseases*

- *Primary sclerosing cholangitis*
- *Primary biliary cirrhosis*
- *Cholestasis of pregnancy*
- *Bile duct obstruction from tumors or gallstones*
- *Hepatitis C*



Causes of Pruritus

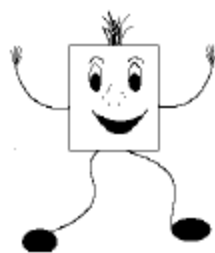
- Liver disease – cholestatic liver disease
- Skin diseases – dermatitis, psoriasis, urticaria
- Kidney disease – end-stage renal disease
- Blood disease – iron deficiency, lymphoma
- Endocrine diseases – diabetes, thyroid disease
- Infectious diseases – scabies, HIV, fungal
- Autoimmune disorders – scleroderma, Sjogren's
- Neurologic disorders – multiple sclerosis, stroke
- Psychogenic disorders – depression, anorexia

Cholestatic Pruritus

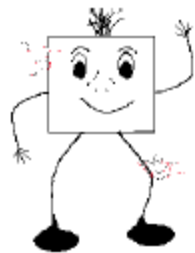
- Occurs in 20-30% of patients with cholestatic liver disease
- Fluctuates in severity
- Generally worse at bedtime
- Potential to drive significant others crazy

Etiology of Cholestatic Pruritus

- Bile acids
- Endogenous opioids
- Lysophosphatidic acid and autotaxin



0
Comfortable,
no itch



1
Itches a little;
does not interfere
with activity



2
Itches more;
sometimes
interferes
with activity

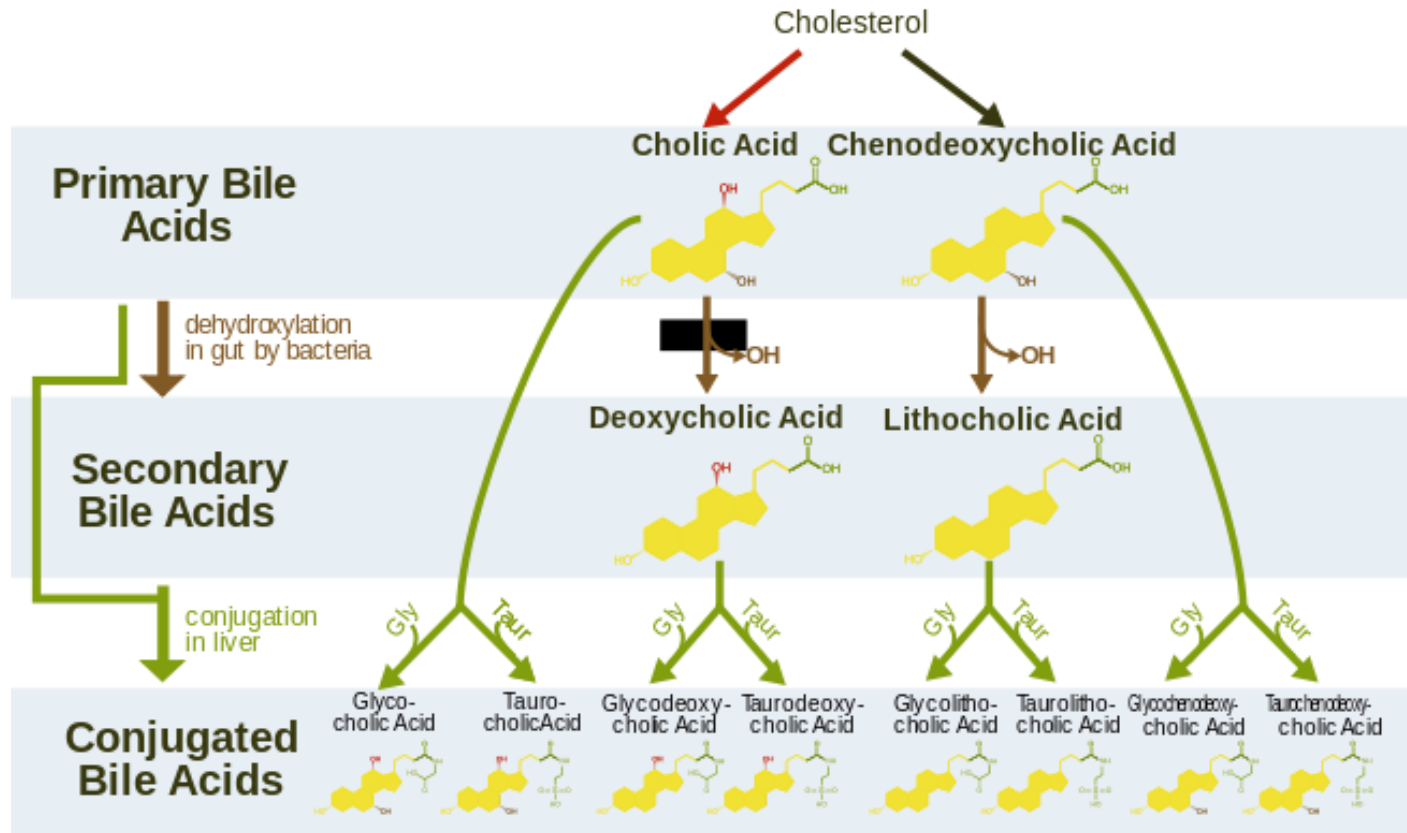


3
Itches a lot;
difficult to be
still, concentrate



4
Itches most terribly;
impossible to sit
still, concentrate

Bile Acids

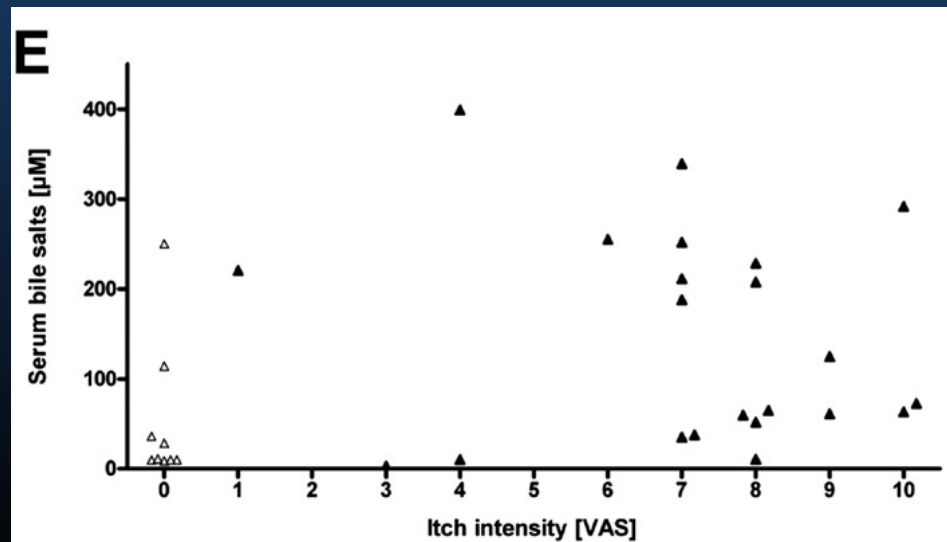


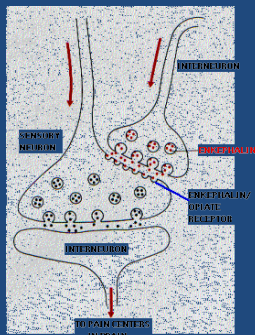
Function of Bile Acids

- Elimination of cholesterol from the body
- Elimination of bilirubin (metabolism of red blood cells)
- Absorption of fat soluble vitamins
- May have role in triglyceride and glucose metabolism and liver growth

Role of Bile Acids in Pruritus

- 1960's demonstrated that bile acid binders relieved itching
 - Assumed retention of bile acids in the skin
- Poor correlation of bile acids in skin and itching





Role of Endogenous Opioids

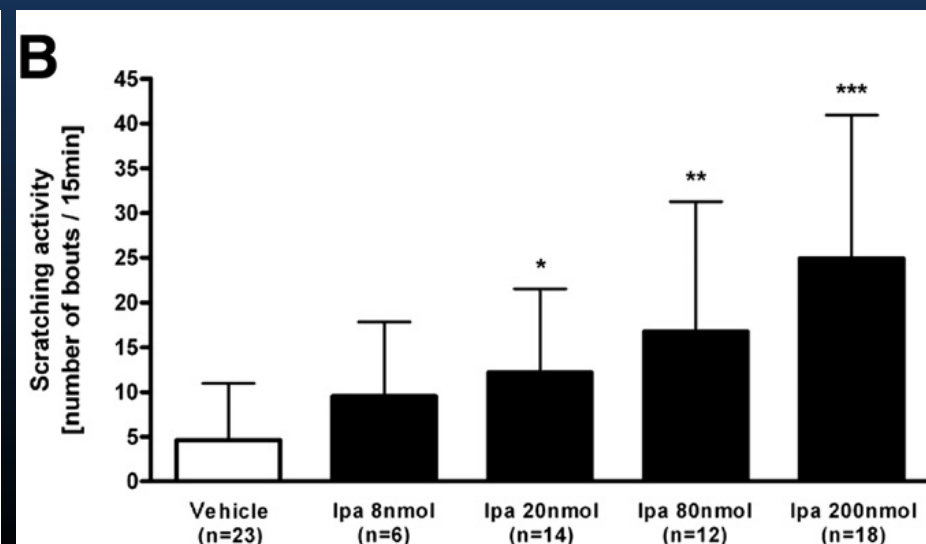
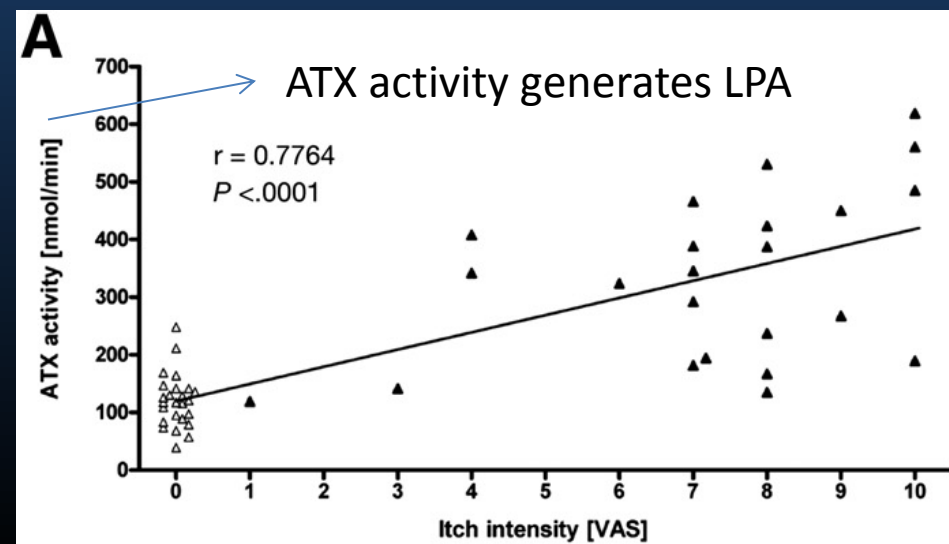
- Noted that narcotic medications makes pruritus worse
- Agonist activity at the *mu* opioid receptor can cause pruritus in normal people
- Endogenous opioid levels are elevated in cholestatic liver disease
 - Improvement in pruritus with blocking opioid receptor

Lysophosphatidic acid (LPA)

- Autotaxin (ATX) required for angiogenesis and neuronal development
- ATX important in generation of LPA
- LPA is small, potent bioactive phospholipid with variety of effects in many cell types
 - Cytoskeletal (re)organization and cell migration
 - Cytokine production
 - Platelet activation
- Plays crucial role in neuropathic pain
 - Reprogramming of gene expression in different types of nerve fibers

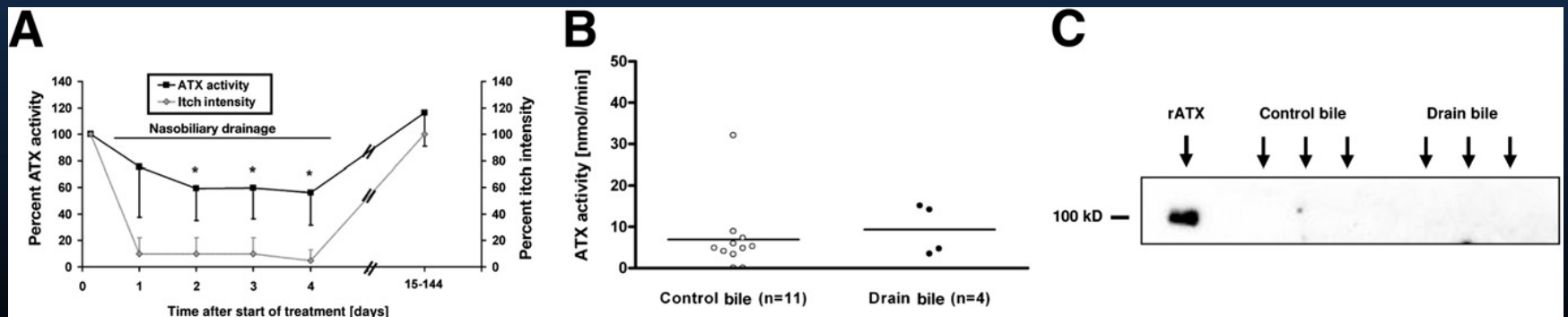
Role of LPA in Cholestatic Pruritus

- Levels of LPA are markedly increased in serum of patients with cholestatic pruritus
 - Serum levels closely correlate with itch intensity
 - Intradermal injection induces scratch behavior in mice



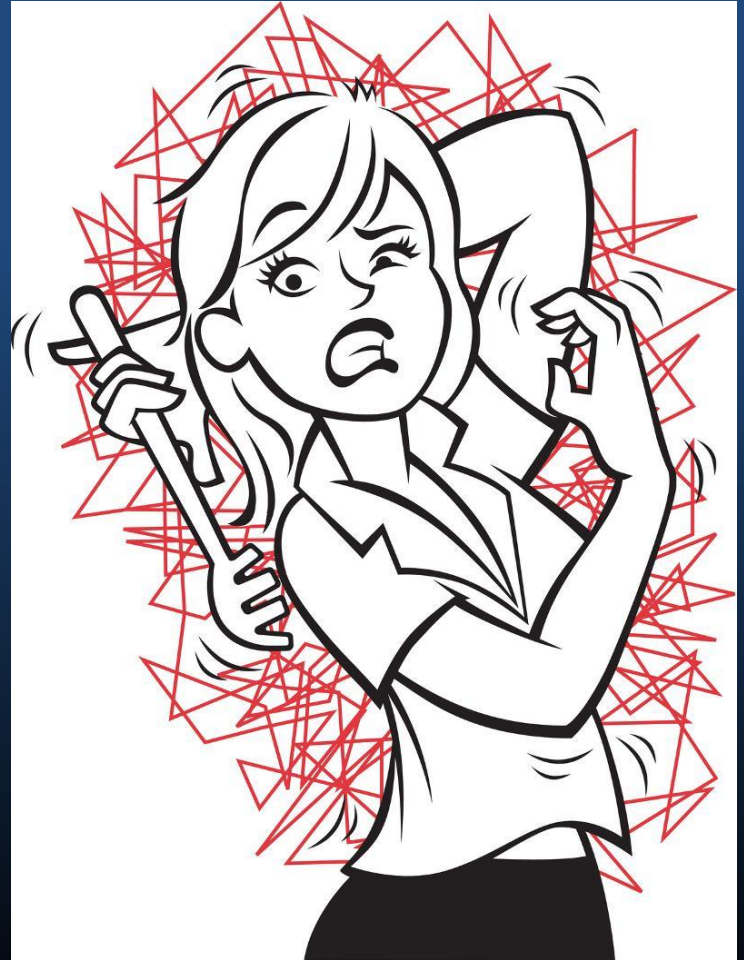
Interaction of ATX/LPA and Bile Salts

- PBC patients with severe pruritus
- Nasobiliary drainage for 2-7 days leading to reduction in pruritus
- Interestingly lead to reduction in ATX activity
- Finding not due to reduction of ATX in bile



Future Novel Treatment Strategies

- ATX inhibitors
- LPA receptor blockers

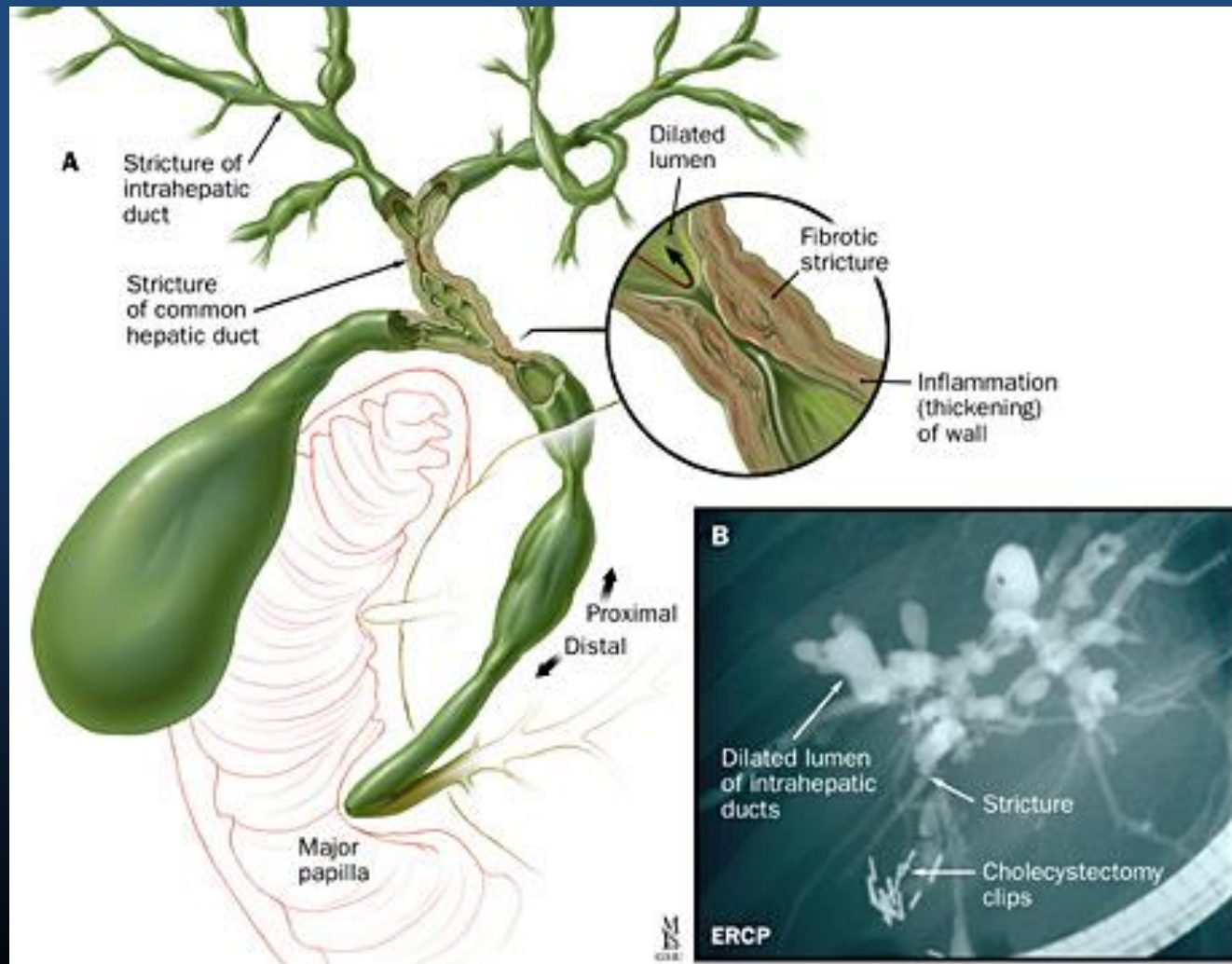


Simple Treatments for Pruritus

- Skin moisturizers (especially in Denver!)
 - Dry skin can cause or exacerbate
- Avoid hot showers
- Avoid narcotics
- Cool environment
- Avoid stress
- Avoid physical interventions
 - Itch-scratch cycle
- Topical therapy
 - Sarna lotion
 - Hydrocortisone cream
 - Ice packs
 - Topical anesthetics
 - Antihistamines



First Line Therapy for Cholestatic Pruritus: Relieve Biliary Obstruction



Treatments of Cholestatic Pruritus

- Bile acid resin binders
 - Cholestyramine
 - Colestipol
- Ursodiol
 - Useful in intrahepatic cholestasis of pregnancy
- Rifampin
- Phenobarbital
- Opioid antagonists
 - Naloxone
 - Naltrexone
- Serotonin-receptor antagonists (sertroline)
- Plasmaphoresis/MARS
- Steroids
- UV light



Bile Acid Binders

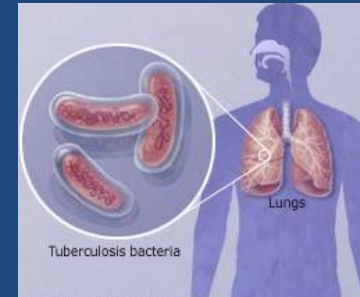
Cholestyramine/Colestipol

- Non-absorbable resin binding bile acids
- Used to treat elevated cholesterol, bile acid diarrhea after cholecystectomy
- Initial dose 4 gms 1-2 times daily → 3x/day
- Side effects:
 - Nausea, bloating, constipation
 - Binds other medications (digoxin, urso, warfarin, propranolol, thiazide diuretics)
 - Take 2-4 hours before/after other meds



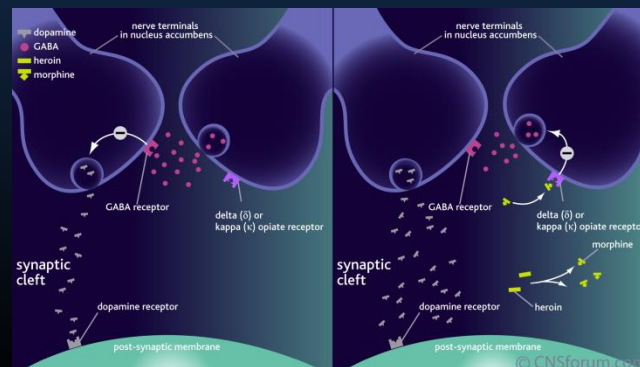
Rifampin

- Anti-tuberculous drug
- Mechanism of action unclear
 - Competes with bile acids for hepatic uptake
 - Induce enzymes in liver promoting reduction of toxic bile acids
- Initial dose: 300 -600 mg/day
- Side effects: acute hepatitis so caution in advanced liver disease
- Drug interactions



Opioid antagonists

- Blocking opioid receptor – central action
- Doses:
 - Naloxone 0.4mg IV then 0.2mcg/kg/min x 24 hrs
 - Naltrexone 12.5-50 mg daily
 - Nalmefene 60-120 mg daily
- Can't take with narcotics or history of chronic pain



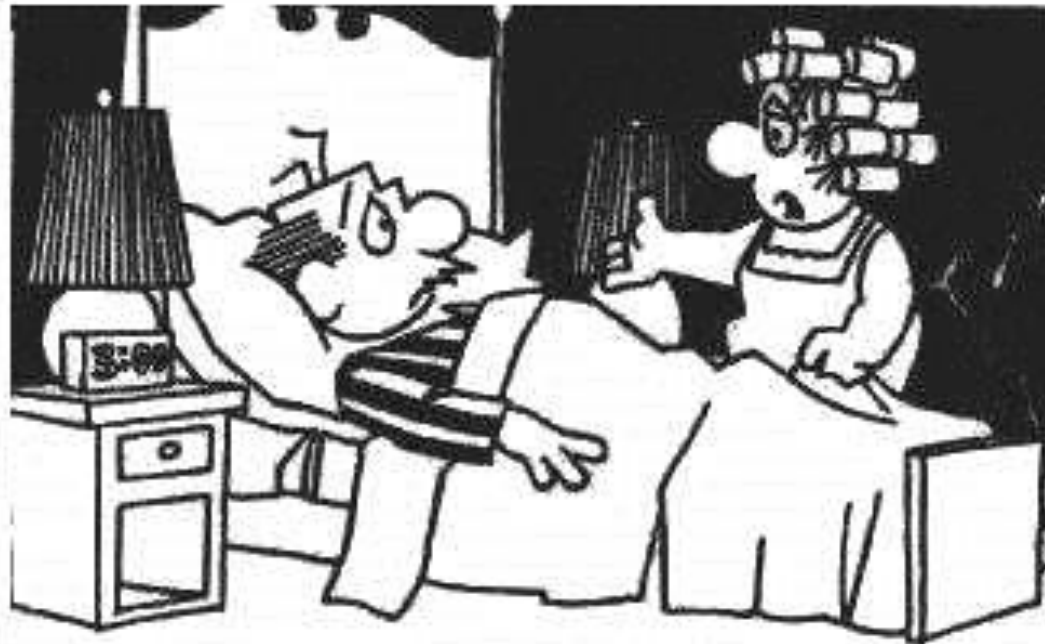
AASLD Guidelines for Treating Pruritus

1. Bile acid sequestrants
2. Rifampin 150-300mg twice daily
3. Naltrexone 50 mg daily
4. Sertraline 75-100 mg daily



Liver transplantation is indication for severe, incapacitating and refractory pruritus

Sleep Disorders



"No wonder you have insomnia . . .
lying there awake all night."



International Classification of Sleep Disorders

- Insomnia
 - Difficulty initiating or maintaining sleep
- Sleep related breathing disorders
 - Obstructive sleep apnea, hypoventilation
- Central disorders of hypersomnolence
 - Medications, stroke, heart failure, renal failure
- Circadian rhythm sleep-wake disorders
 - Shift work, jet lag, hepatic encephalopathy
- Parasomnias
 - Undesirable physical or emotional experiences during sleep
- Sleep related movement disorders
 - Restless leg syndrome
- Other sleep disorders

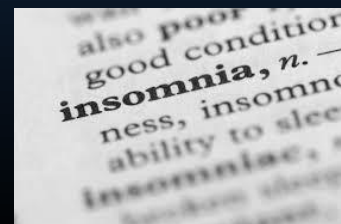
Sleep Disorders in Cirrhosis



- Sleep disorders common with cirrhosis
 - 2/3rd report sleep-wake abnormalities
 - Disturbed night sleep
 - Delayed sleep
 - Excessive day-time sleepiness
 - 70% cirrhosis classified as “poor sleepers” using validated Pittsburgh Sleep Quality Index
 - Often associated with hepatic encephalopathy (HE)
 - Half of patients do not have HE (undiagnosed?)
- Significant impact on quality of life and physiological well-being

Cirrhosis Associations with Sleep Disorders

- Higher prevalence of SD with more advanced CTP score
- Low albumin levels
 - Free forms of albumin-bound toxins may cross blood-brain barrier
- Patients with cirrhosis go to bed later, sleep later
- Animal models show derangements in sleep patterns



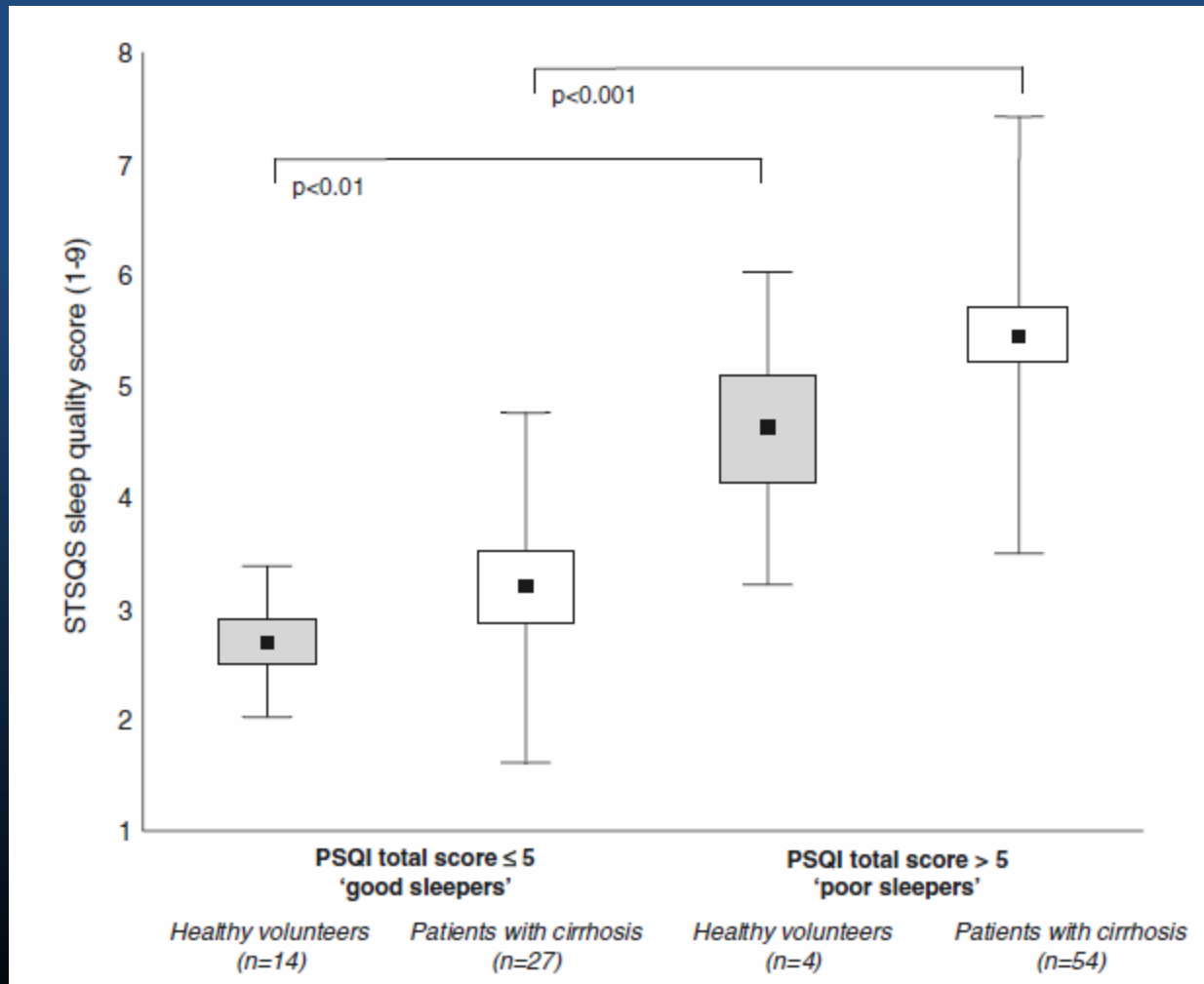
Sleep Timing and Sleep Quality Screening Questionnaire

What time do you usually go to bed?	
What time do you usually start trying to sleep?	
How long does it take you to fall asleep on average?	
How many times do you usually wake up?	
What time do you usually wake up <i>in the morning</i> ?	
What time do you usually get up?	

How would you rate your usual quality of sleep?

1 2 3 4 5 6 7 8 9
Best sleep ever Worst sleep ever

Comparison of STSQS Questionnaire with Pittsburg Sleep Quality Index

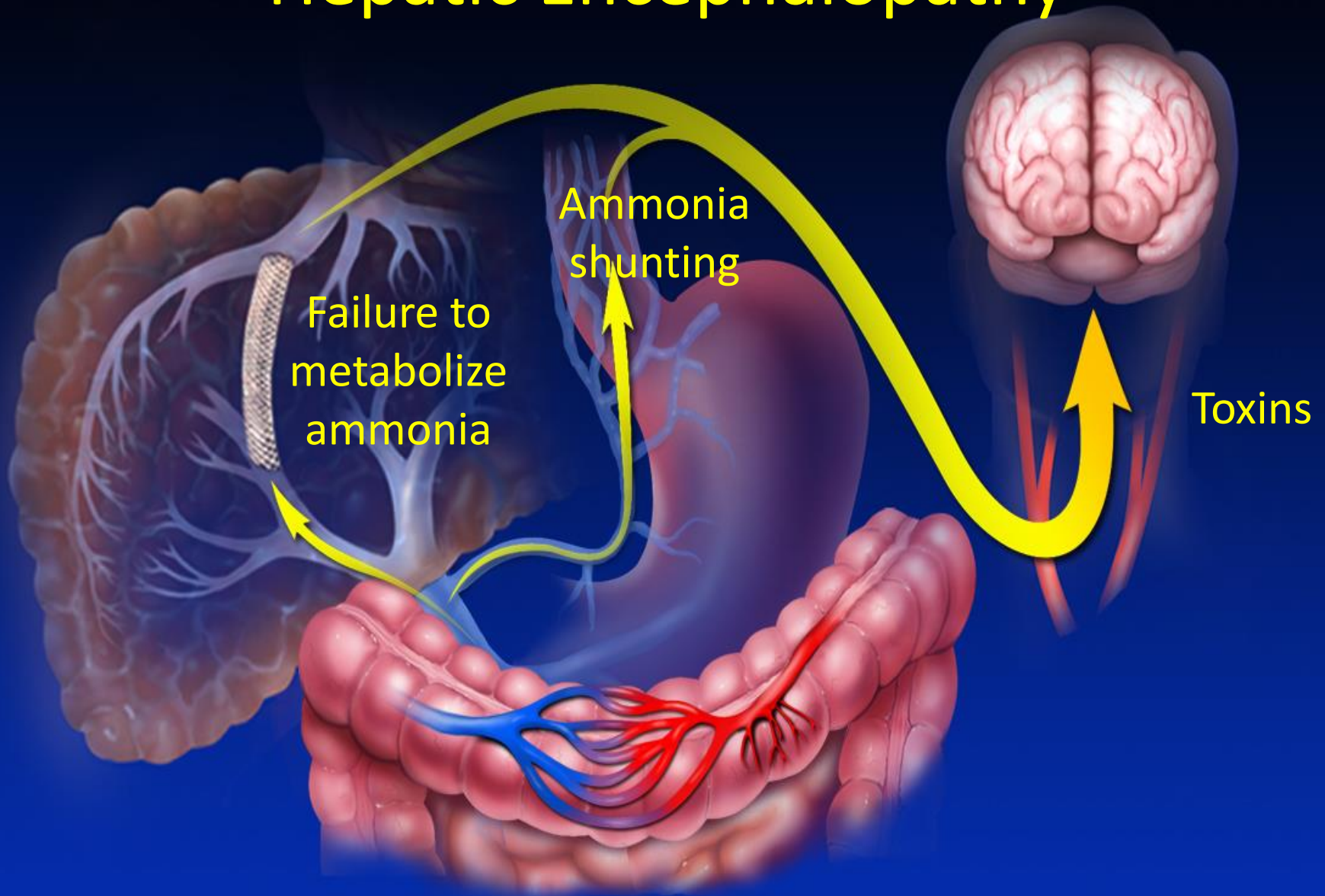




Hepatic Encephalopathy

- Neuropsychiatric complication of cirrhosis
- Result of:
 - Portosystemic shunting
 - Liver insufficiency
- Failure to metabolize neurotoxic substances
 - Ammonia

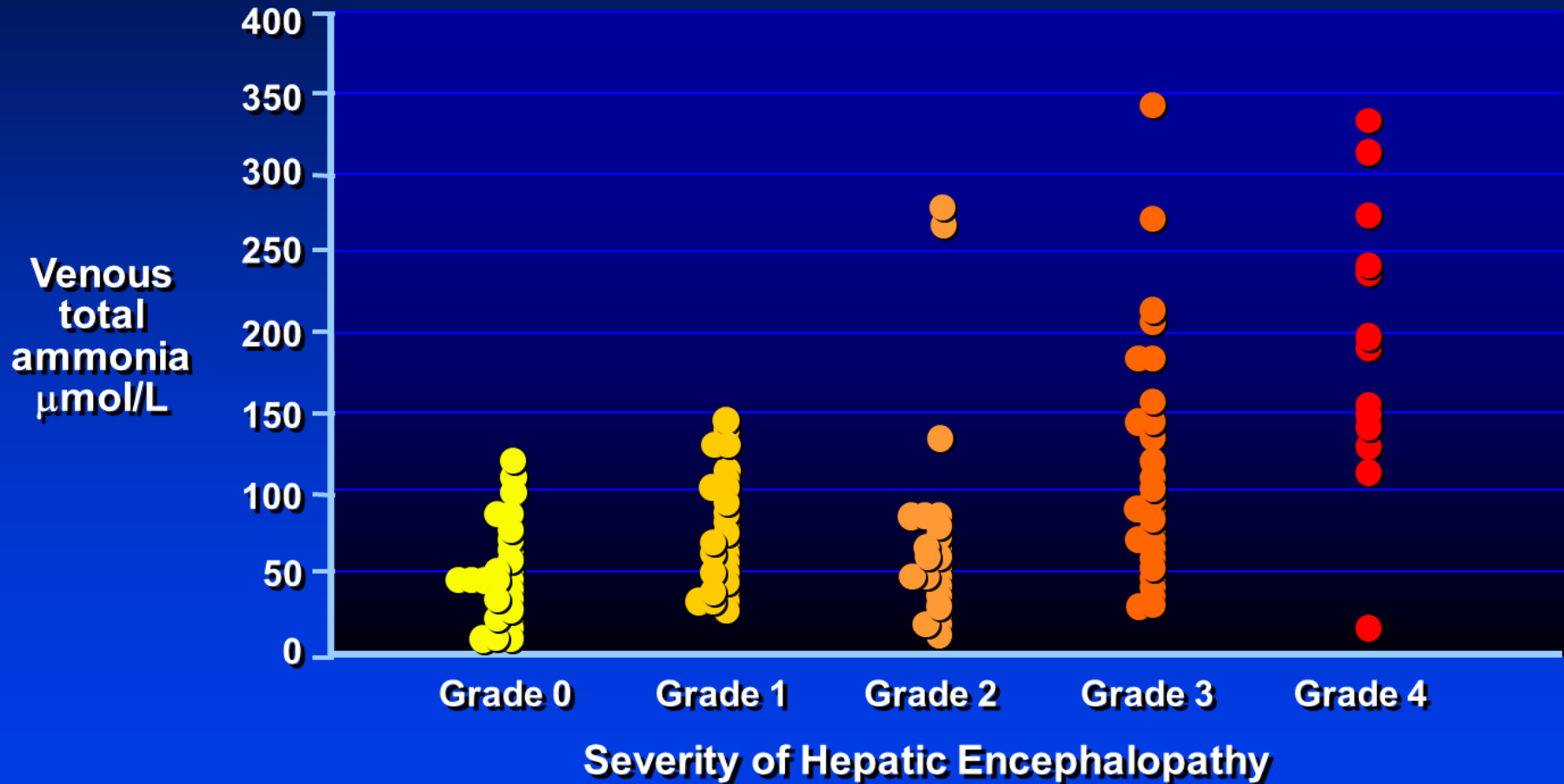
Pathogenesis of Hepatic Encephalopathy



Hepatic Encephalopathy is a Clinical Diagnosis

- Clinical history and exam are most important
- Ammonia levels are unreliable
 - Poor correlation with diagnosis or severity
- Measurement of ammonia levels are not necessary
- Clinical research tools
 - Number connection test

Poor Correlation of Ammonia Levels With Presence or Severity of Encephalopathy



Hepatic Encephalopathy Precipitants



Excess protein

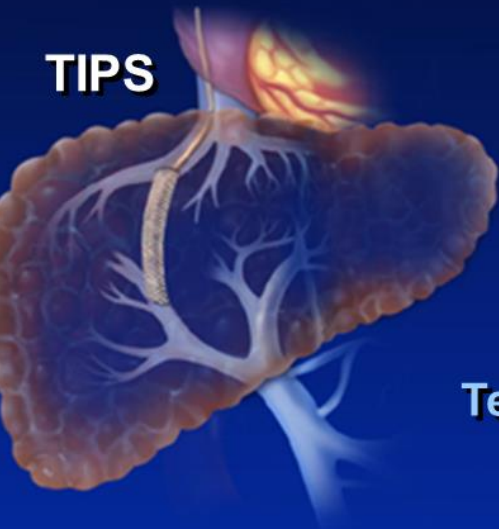


GI bleeding



Sedatives /
hypnotics

TIPS



Temp



Infections



Diuretics



↓ Serum K⁺
Plasma volume

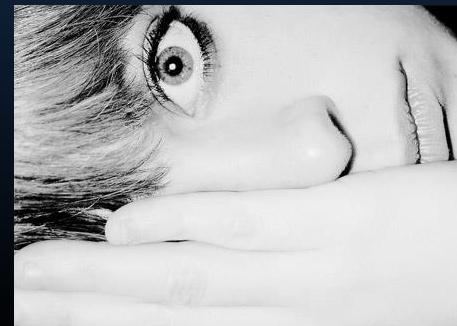
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Azotemia

Treatment of Hepatic Encephalopathy

- Identify and treat precipitating and reversible factors:
 - Infection
 - GI bleeding
 - Renal failure
 - Sedatives
 - Constipation
- Lactulose – goal 3 bowel movements/day
- Rifaximin – non-absorbable antibiotic
- L-ornithine L-aspartate
- Zinc

Recommendations For Improved Sleep Hygiene

- Do not eat 3 hour prior to bed
- Unwind from day's tensions 1 hour before bed
- Avoid screen time (TV, iPhone, computer) before bed
- Warm milk (tryptophan) or herbal tea
- Keep bedroom cool
- Soft sheets
- Bed is for sleep only!
 - Don't fall asleep in 20 minutes get out of bed and read or do something relaxing
- Avoid naps during day (20-30 minutes early afternoon is okay)
- No alcohol
- No caffeine after noon
- Exercise daily (not in the evening)



END