Current Concepts and Management of the Pruritus of Cholestasis

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Cholestasis

- **Definition**
  - **Impaired secretion of bile**
    - **Consequence of most liver diseases**
- **Accumulation in tissues of substances excreted in bile**

Causes of Cholestasis

- **Intrahepatic**
  - **Benign recurrent intrahepatic cholestasis (BRIC)**
  - **Alagille's syndrone**
  - **Drug toxicity**
  - **Primary biliary cirrhosis**
  - **Primary sclerosing cholangitis**
  - **Pregnancy**
  - **α–1 antitrypsin deficiency**
  - **Granulomatous disease**
  - **Lymphoma**
  - **Chronic hepatitis C infection**
- **Extrahepatic**
  - **Obstruction**
    - **Stones**
    - **Strictures (e.g. post-cholescystectomy)**
    - **Malignancy**

Pruritus in Cholestasis

- Complication of cholestasis
- Etiology unknown
- Treatments not universally satisfactory
- Indication for liver transplantation

Pruritus of cholestasis

- May be intermittent
- Generalized or localized
- Worse in the premenstrual period in 25% of subjects

Pruritus in PSC

- **Due to :**
  - **Cholestasis**
  - **Cholangitis**
- **Infection must be excluded and treated with antibiotics**

On the Pruritogen(s) of Cholestasis

- Made in the liver
- Excreted in bile
- Accumulate in tissues due to cholestasis
- Direct correlation between serum markers of cholestasis and pruritus not documented

Substances and Neurotransmission Systems of Interest In Pathogenesis of Pruritus

- Bile Acids
- Histamine
- Serotonin
- Substance P
- Autotaxin
- Endogenous Opioids

Bile Acids

- Intradermal injection associated with pruritus
  - Not a model of pruritus of cholestasis
- Pruritus is intermittent and independent from concentrations of serum bile acids
  - Specific profile may be relevant

Bile acids (II)

- Study of obeticholic acid for treatment of primary biliary cirrhosis
  - Side effect: pruritus
- Recent study in animals revealed that some bile acids can stimulate neurons that can fruther stimulate opioid pathways

Histamine

- **Serum histamine concentration increases in cholestasis and pruritus**

However,

- **Skin of patients with cholestasis and pruritus devoid of histamine-related signs**
- **Antihistamines are associated with sedation and may result in some relief of pruritus by that mechanism**

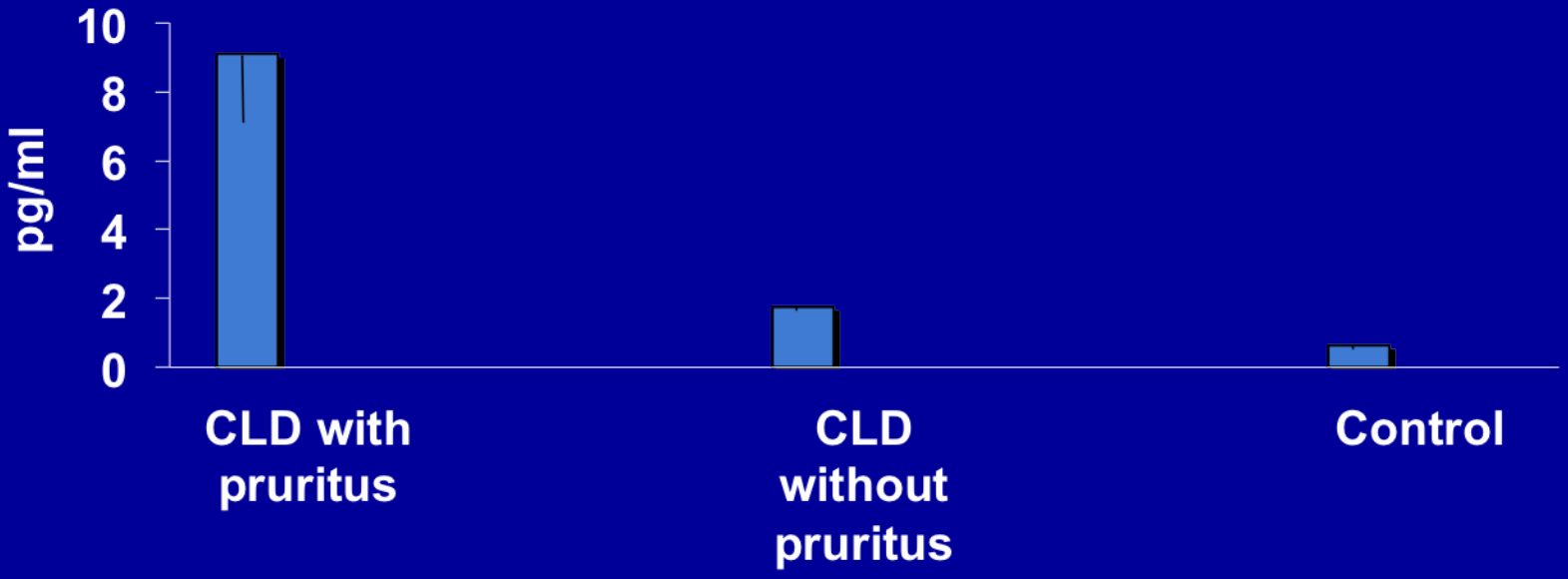
Serotonin Neurotransmission

- **Involved in mediation of nociception**
  - **Ondansetron, type 3 serotonin receptor antagonist**
  - **Serotonin re uptake inhibitors reported to relief pruritus**

Substance P Neurotransmission

- **Substance P is:**
  - **Excitatory substance that realtes to inflammation, pain, and possibly pruritus**
- **Substance P concentrations in serum are high in patients with liver disease and pruritus**

Mean Serum Concentrations of Substance P in Patients with Chronic Liver Disease



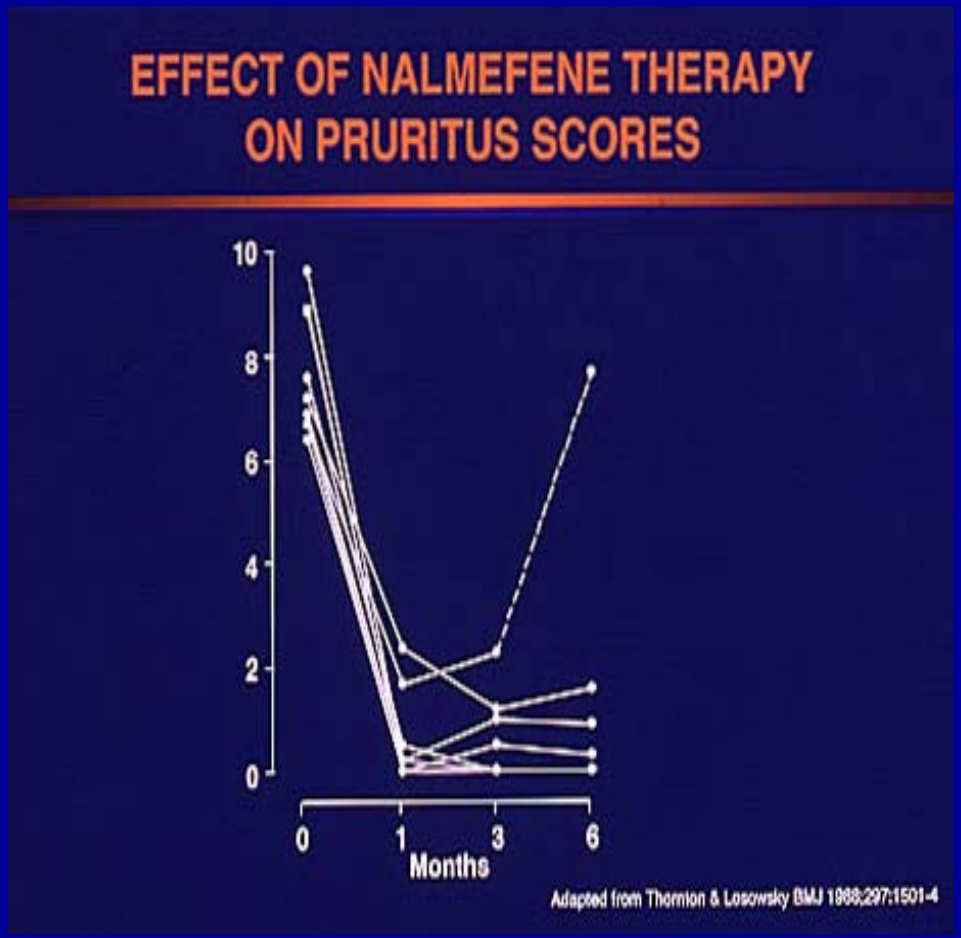
CLD w P, N: 13
CLD w/o P, N: 17
Control: N:12

Trivedi and Bergasa J Hepatol 2010

Autotaxin

- Autotaxin is the enzyme that activates lipophosphatidic acid (LPA)
- It was reported to be high in patients with cholestasis and pruritus and not in patients with pruritus from other conditions
- It decreases in association with pruritus relief by partial diversion of bile, and to increase when pruritus returns

Increased Opioidergic Tone in Cholestasis: Symptoms And Signs Associated With Nalmefene In Patients With Cholestasis



- abdominal pain
- diaphoresis
- insomnia
- lack of concentration
- palpitations
- changes in vital signs

Meaning of the opiate withdrawal like reaction

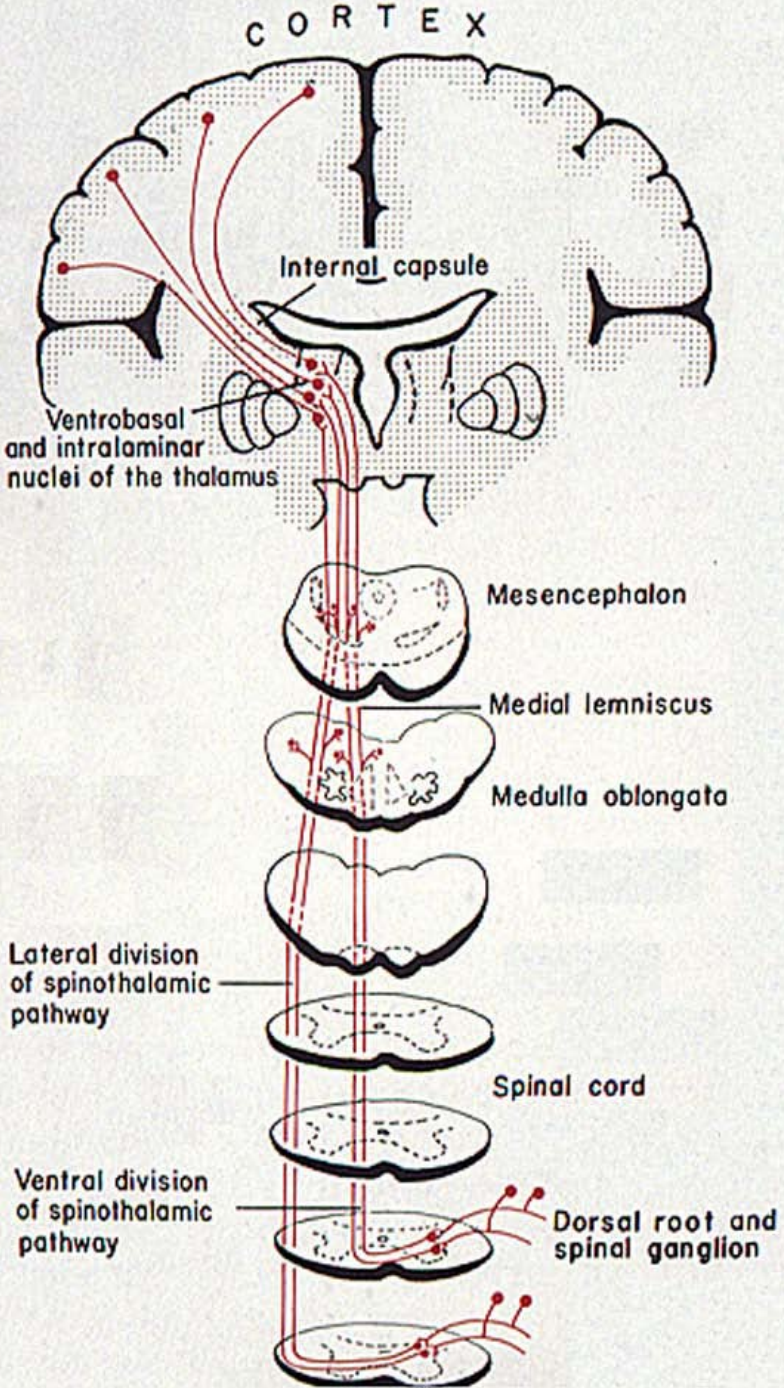
- **Withdrawal reaction occurs when brain used to high concentrations of opiate drugs, i.e. heroin, morphine**
- **In the absence of drugs, a withdrawal like reaction suggests that the subjects have increase in natural opioids in the brain**

Relationship between opioids and pruritus

- Endogenous (natural) opioids exert their effects by binding to opioid receptors and stimulating cellular signals: endogenous analgesia or pain relief
- Opiate drugs and morphine also bind to the opioid receptors: analgesia

Relationship between opioids and pruritus

- Opiate drugs and morphine cause pruritus when given intrathecally (i.e. spinal canal such as epidural treatment of pain)
- This type of pruritus can be relieved and prevented by opiate antagonists, which prevent or counteract the effects of the drugs (e.g. naloxone)


CORTEX
Internal capsule
Ventrobasal and intralaminar nuclei of the thalamus
Mesencephalon
Medial lemniscus
Medulla oblongata
Lateral division of spinothalamic pathway
Spinal cord
Ventral division of spinothalamic pathway
Dorsal root and spinal ganglion

Hypothesis

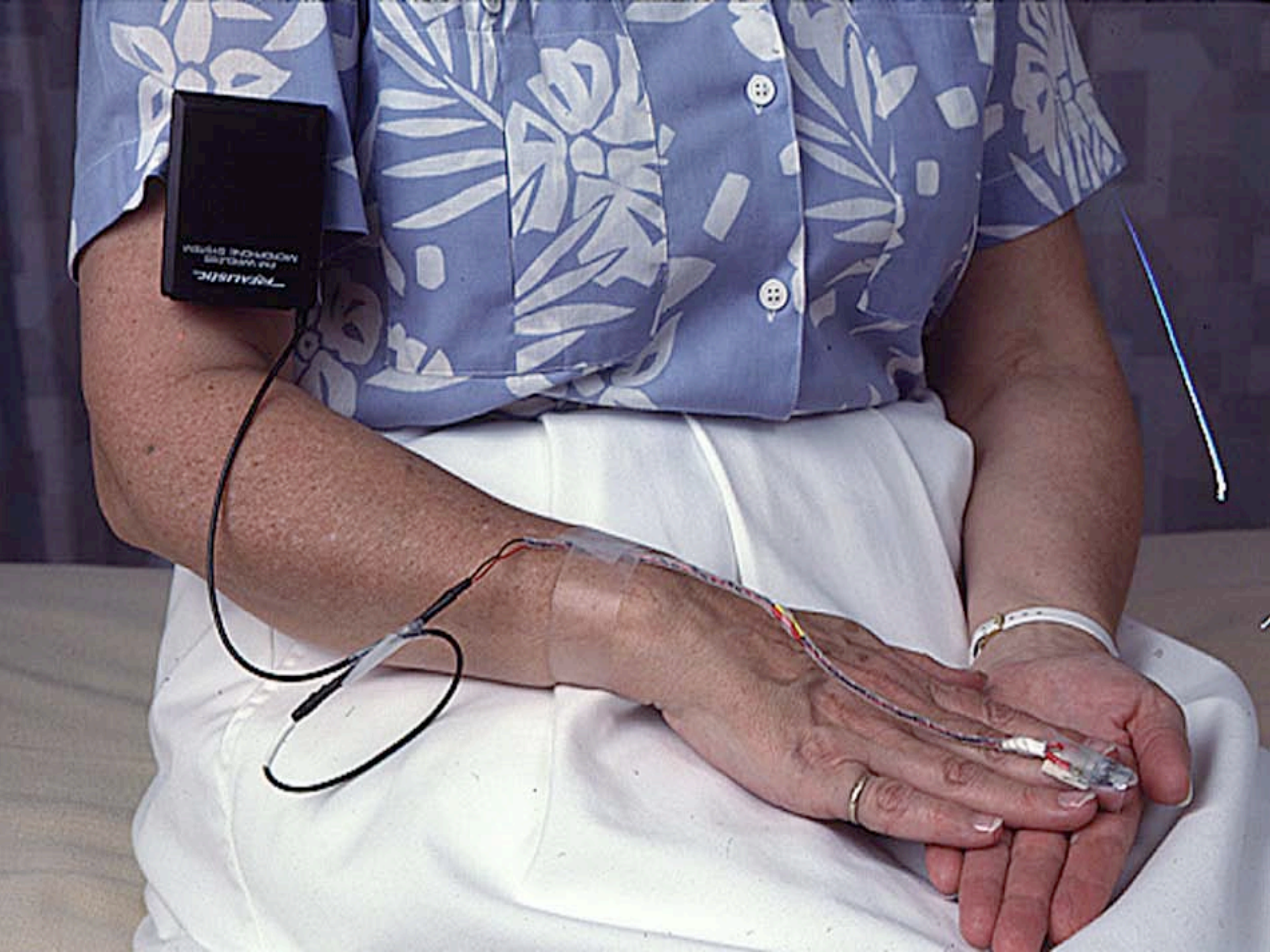
- **Increased central opioidergic tone contributes to the pruritus of cholestasis**
  - » **Jones and Bergasa, Hepatology 1990**

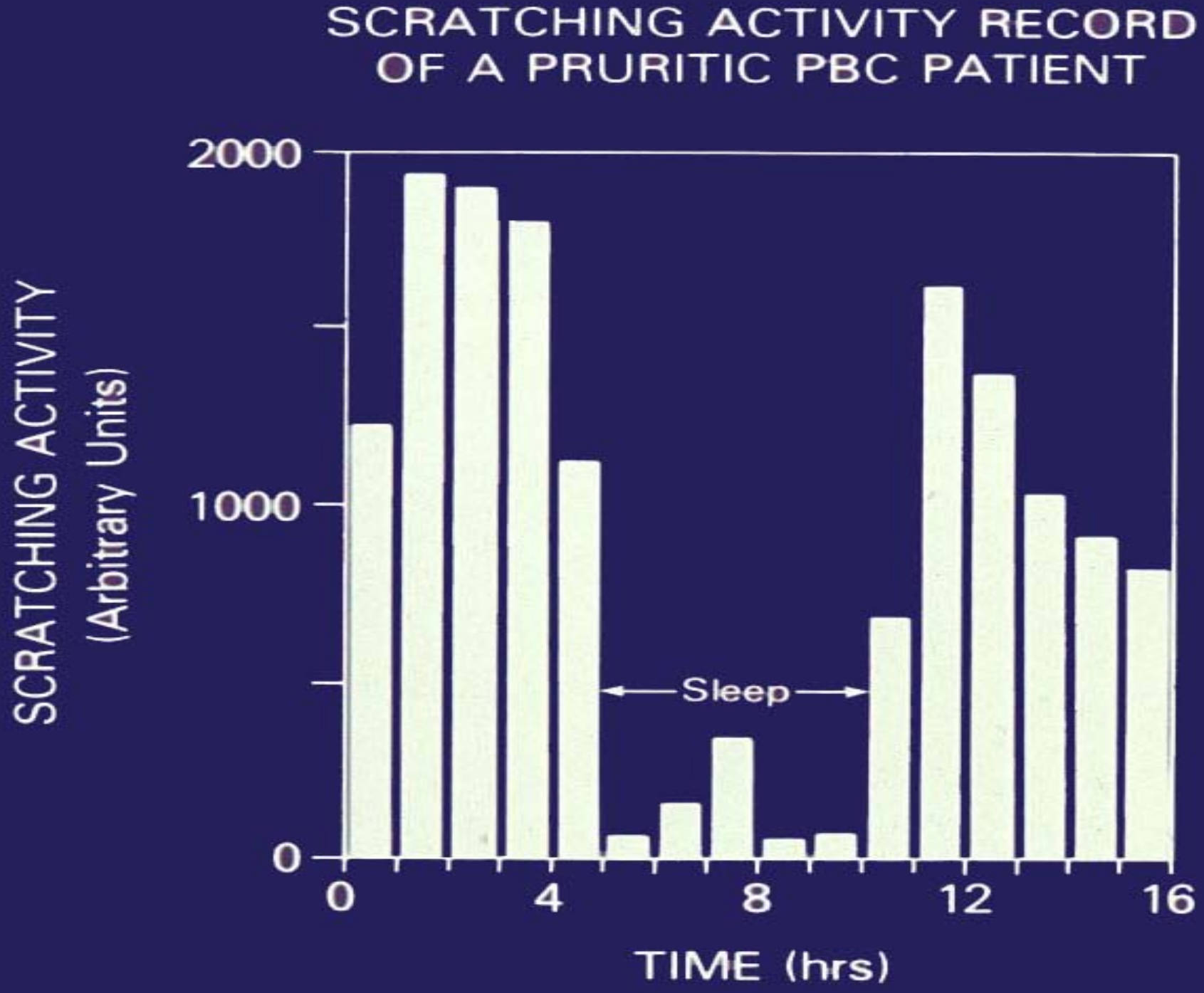
- **If so, opiate antagonists, which prevent the effect of natural opioids and opiate drugs should relieve this type of pruritus and scratching**

Methods to study pruritus

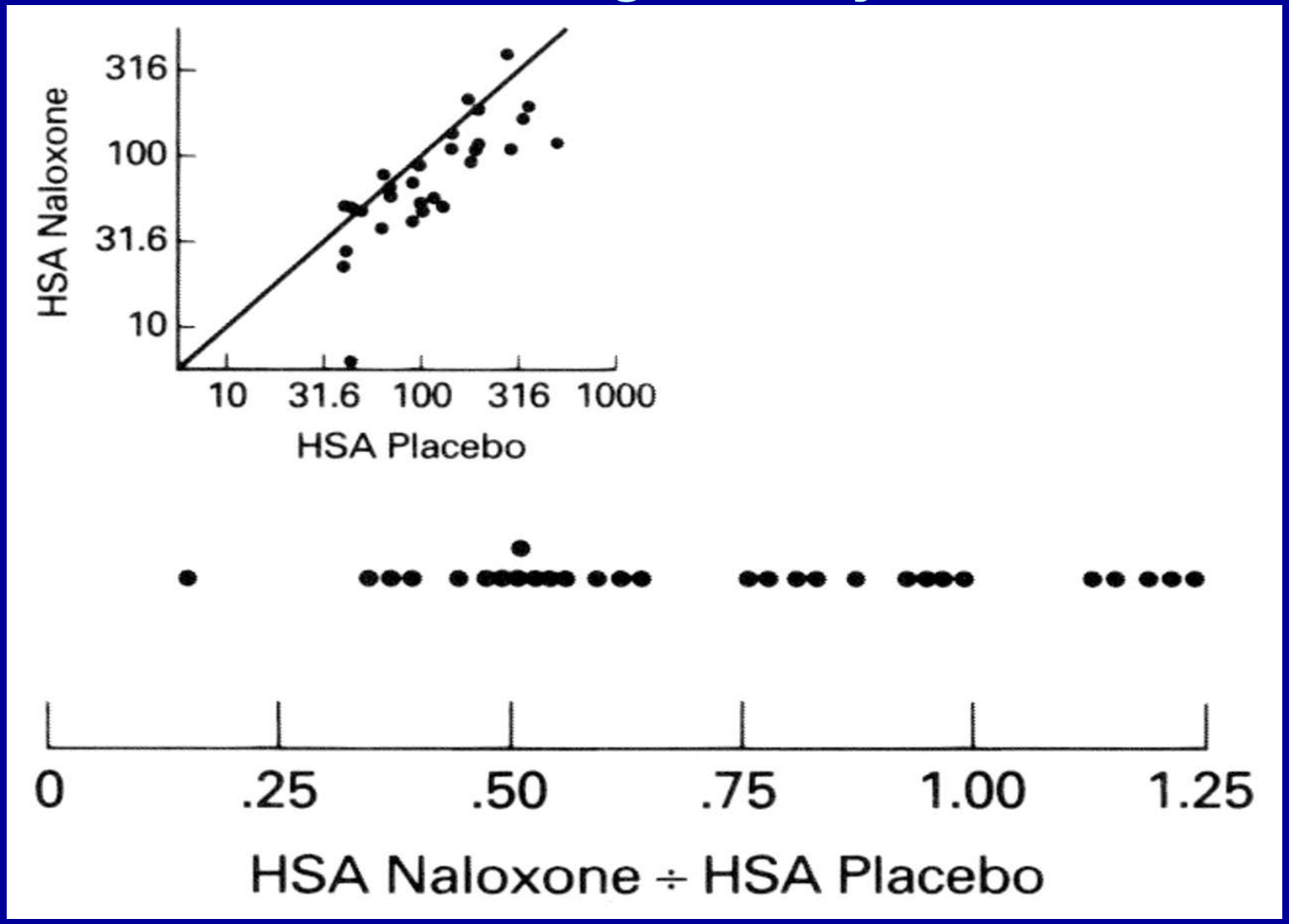
- **Questionnaires and visual analogue scales**

- **Measures of scratching, the behavior that results from itching**




SCRATCHING ACTIVITY RECORD
OF A PRURITIC PBC PATIENT
2000
1000
0
SCRATCHING ACTIVITY
(Arbitrary Units)
Sleep
0
4
8
12
16
TIME (hrs)

Effect of Naloxone Infusions on Hourly Scratching Activity



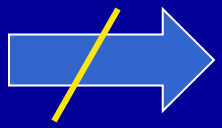
Bergasa et al Ann Int Med 1995

Opiate Antagonists for Treatment of the Pruritus of Cholestasis

- Documented in controlled, randomized, double blind studies that applied behavioral methodology
- Numerous reports on their effectiveness
- A therapeutic alternative in the guideline of pruritus in cholestasis (i.e. PBC)

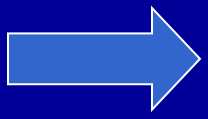
Opiate Antagonists for Pruritus: Safety

- **Opioid withdrawal reaction**



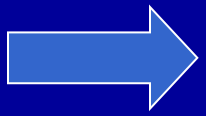
Low doses of opiate antagonists (e.g. IV naloxone (e.g. 0.002 ⇑ microg/kg/min 0.2-0.8 microg/kg/min ⇒ oral naltrexone 12.5- 50 to 100 mg /day (Jones, Neuberger and Bergasa QJM2002)

- **Potential hepatotoxicity at high doses**



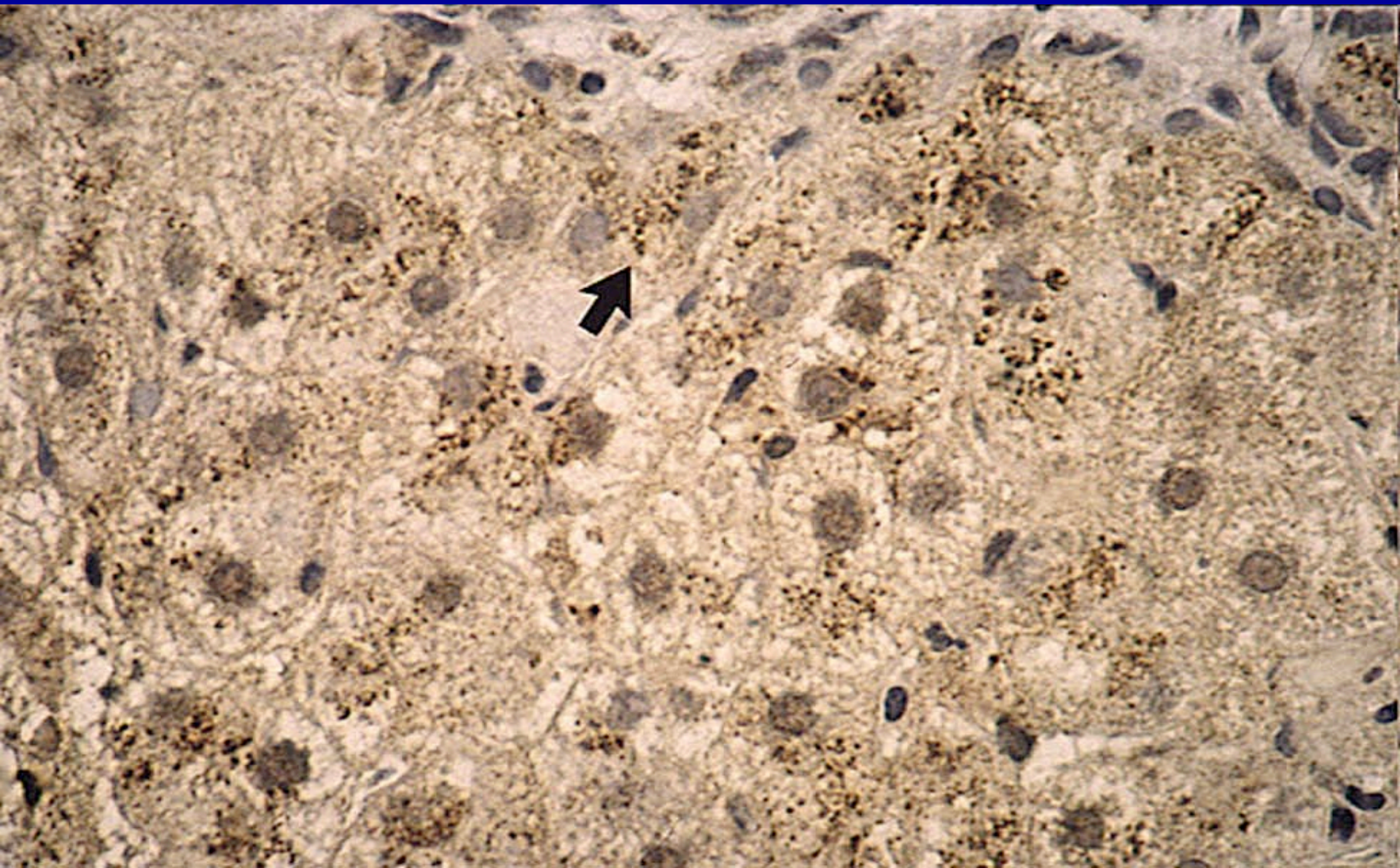
- **Monitoring of liver tests**
- **No hepatotoxicity at short term (Krystal et al NEJM 2001)**

- **Altered metabolism in decompensated disease**



- **Decreased conversion to metabolite but safe (Bertolotti et al JHepatol 1997)**
- **Usually not relevant: pruritus ceases in hepatocellular dysfunction**

Liver Met-enkephalin Immunoreactivity Expression in Primary Biliary Cirrhosis



Management of Pruritus:
Removal of Pruritogen(s) from the Circulation

- **Nonabsorbable resins (presumed mechanism)**
- **Extracorporeal albumin dialysis (MARS)**
- **Plasmapheresis**

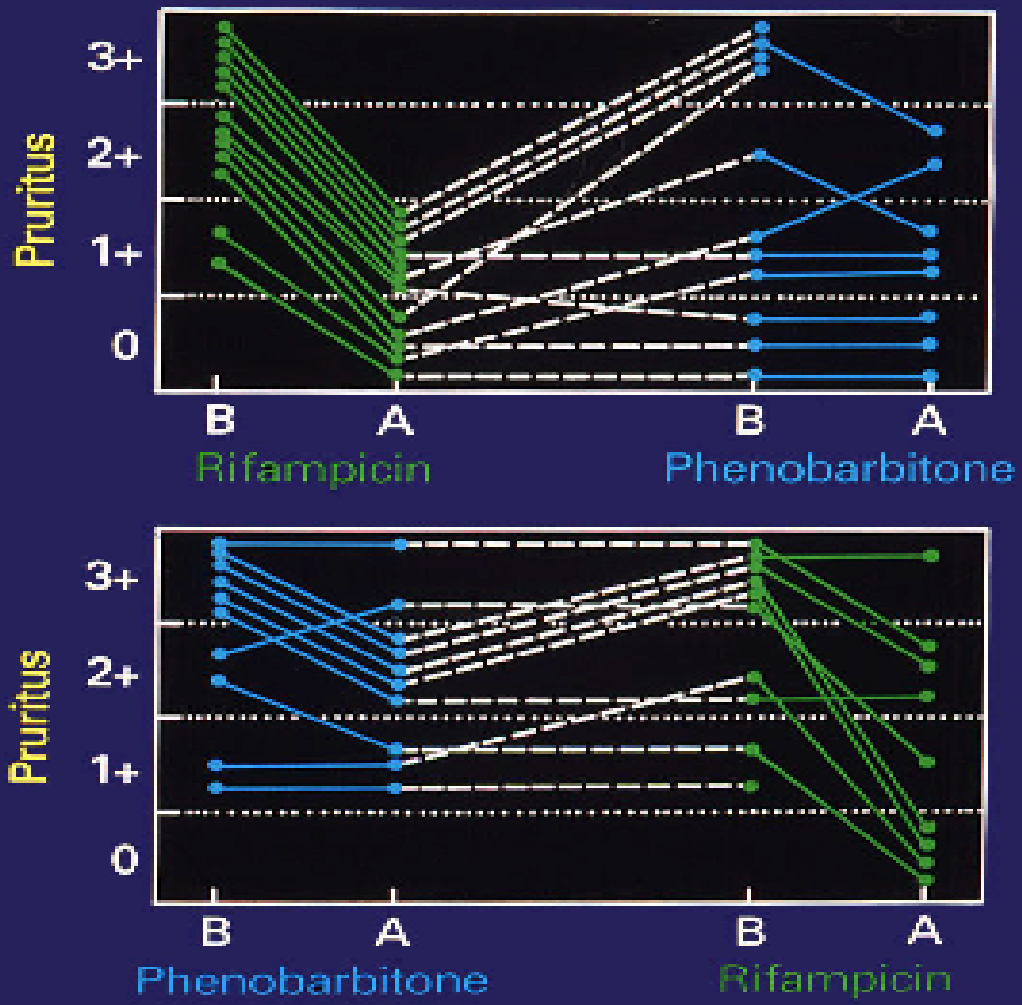
Cholestyramine

- **Rationale: pruritogens that accumulate in gallbladder during overnight fast pour on small bowel after fast in broker**
- **4 g before and after breakfast**
- **4 g with lunch and breakfast if needed, not to exceed 16 g per day**

Management of Pruritus: Antibiotics

- **Metronidazole**
  - **250 mg p.o.BID**
- **Rifampicin**
  - **Agonist at the PXR receptor (e.g. detoxification)**
  - **May have opiate-antagonist activity in vivo**
  - **Doses:**
    - **10 mg/kg P.O. (Bachs et al 1991)**
    - **Hepatotoxicity**

Effects of Rifampicin And Phenobarbitone on The Pruritus Scores of Patients with PBC



From Bachs et al the Lancet, 1989

Management of Pruritus: Neuromodulators

- **Serotonin reuptake inhibitor**
  - **Sertraline 75 mg per day, subjective methodology (Mayo et al Hepatology 2007)**

Management of the Pruritus: Increased Threshold to Nociception

- Pruritus is a nociceptive stimulus; thus, increasing threshold to nociception may decrease pruritus
  - Cannabinoidergic neurotransmission
    - Dronabinol 5- 10 mg p.o. daily
  - Gabaergic neurotransmission
    - Gabapentin in some subjecdts

Other treatments

- **Anesthetics**
  - **Lidocaine**
  - **Propofol**

Anticipated therapies

- **Specific opioid receptor acting agents**

Challenges With The Use Of Opiate Antagonists

- Some patients do not respond to opiate antagonists
- “Tolerance”
- Not desirable to be in an antiopiate state

Kappa agonists

- Nalfurafine approved in Japan for pruritus from kidney disease
- Being studied for pruritus of cholestasis scratching

Available drugs with antipruritic effects

- **Drugs for neuropathy: Lyrica**
- **Substance P antagonists: aprepitant**

Scientific interest in pruritus

- International Forum for the Study of Itch
- Identification of receptors and substances that mediate nerve cell signals interpreted as itch
- Use of imaging studies to study the brain in the state of itch and scratching
- Optimism