What else is new – pain?

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Outline

- ❖ Opioid-related pain (GI tract)
- Narcotic bowel syndrome
- Other causes

- ❖ “Poor man’s methadone”

Narcotic bowel disease

Opioid-induced hyperalgesia 

Opioid-induced bowel dysfunction 

Narcotic bowel syndrome

Rome IV diagnostic criteria:

Must include all of the following

1. Chronic or frequently recurring abdominal pain* that is treated with acute high-dose or chronic narcotics

** Pain must occur most days*

2. The nature and intensity of the pain is not explained by a current or previous GI diagnosis**

*** A patient may have a structural diagnosis (e.g. inflammatory bowel disease, chronic pancreatitis), but the character or activity of the disease process is not sufficient to explain the pain*

Narcotic bowel syndrome

Rome IV diagnostic criteria:

3. Must include two or more of the following

a). The pain worsens or incompletely resolves with continued or escalating dosages of narcotics

b). There is a marked worsening of pain when the narcotic dose wanes and improvement when narcotics are re-instituted (soar and crash)

c). There is progression of the frequency, duration, and intensity of pain episodes

Narcotic bowel syndrome

Epidemiology:

4-6% patients on long-term opioids

Female

Well-educated

Original pain moderate-to-severe

Psychological problems

Disabled / unemployed (health reasons)

Narcotic bowel syndrome

Aetiology:

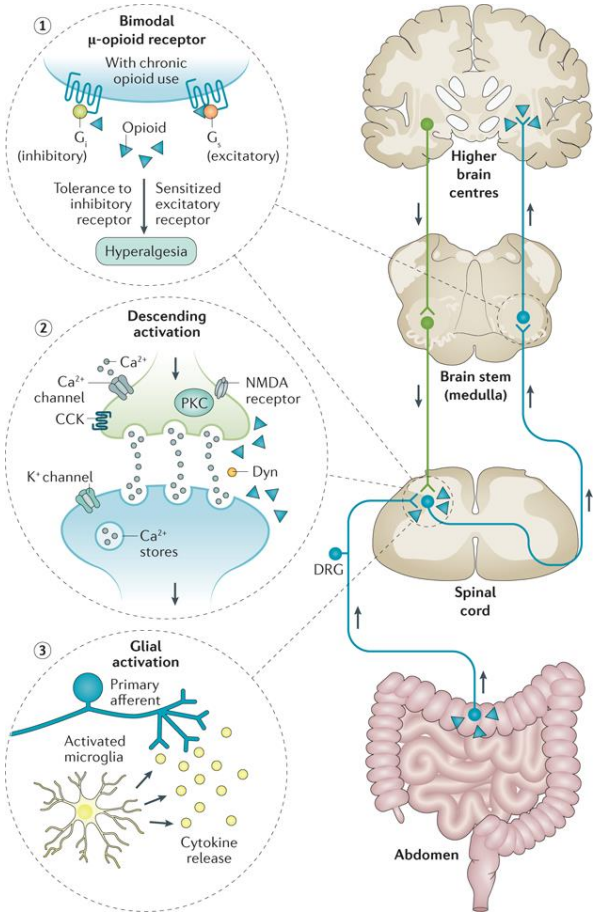
[MEDD > 50-75 mg]

Unclear

Centrally mediated disorder

Multiple potential mechanisms

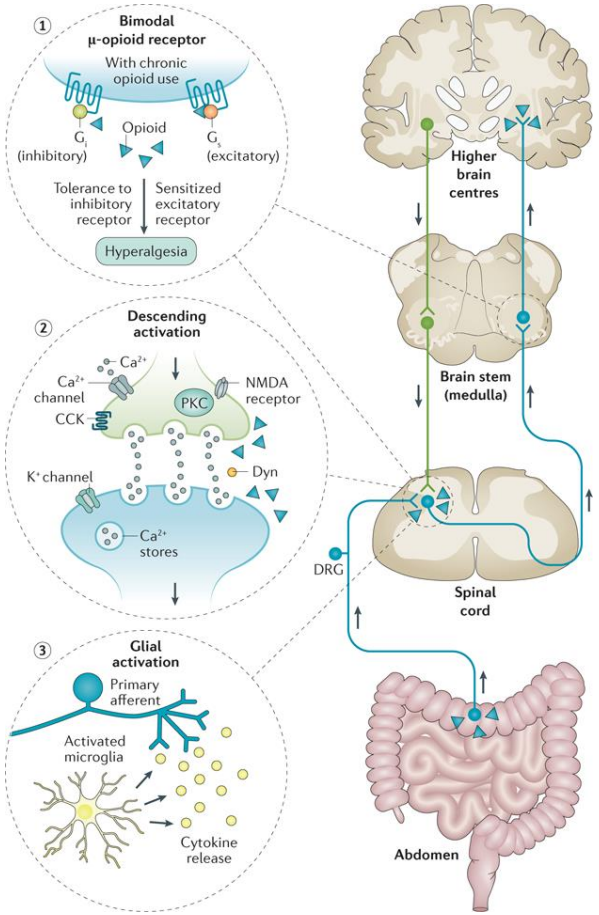
Narcotic bowel syndrome



The bimodal opioid receptor switches from an inhibitory to an excitatory G protein state with chronic opioid exposure (1).

Activation of descending pain pathways is mediated by several mechanisms including cholecystokinin (CCK) and release of dynorphin (Dyn), activation of calcium (Ca^{2+}) and potassium (K^+) channel-mediated membrane hyperexcitability, and protein kinase C (PKC)-induced increase in presynaptic *N*-methyl-D-aspartate (NMDA) receptor activation. On the presynaptic side, opioids paradoxically activate ‘on cells’ projecting from the rostral ventromedial medulla leading to increased dynorphin release. Opioids also activate NMDA receptors, which in turn can cause an influx in calcium and potassium through activated channels leading to increased PKC. These mechanisms sensitize the postsynaptic neuron to pain (2).

Narcotic bowel syndrome



Opioids induce the immune-system-related glial cells to release pro-inflammatory cytokines into dorsal horn of the spinal cord (3). DRG, dorsal root ganglion.

Narcotic bowel syndrome

Clinical features:

*Abdominal pain – starts after 14-28 days; constant / intermittent; colicky / burning; “end-of-dose pain” / (aggravated by eating); relieved by opioids (temporarily)

Nausea

Vomiting (periodic)

Abdominal distension

Constipation

Narcotic bowel syndrome

Management:

Explanation*

Non pharmacological interventions

Non-opioid analgesics – TCAs, SNRIs

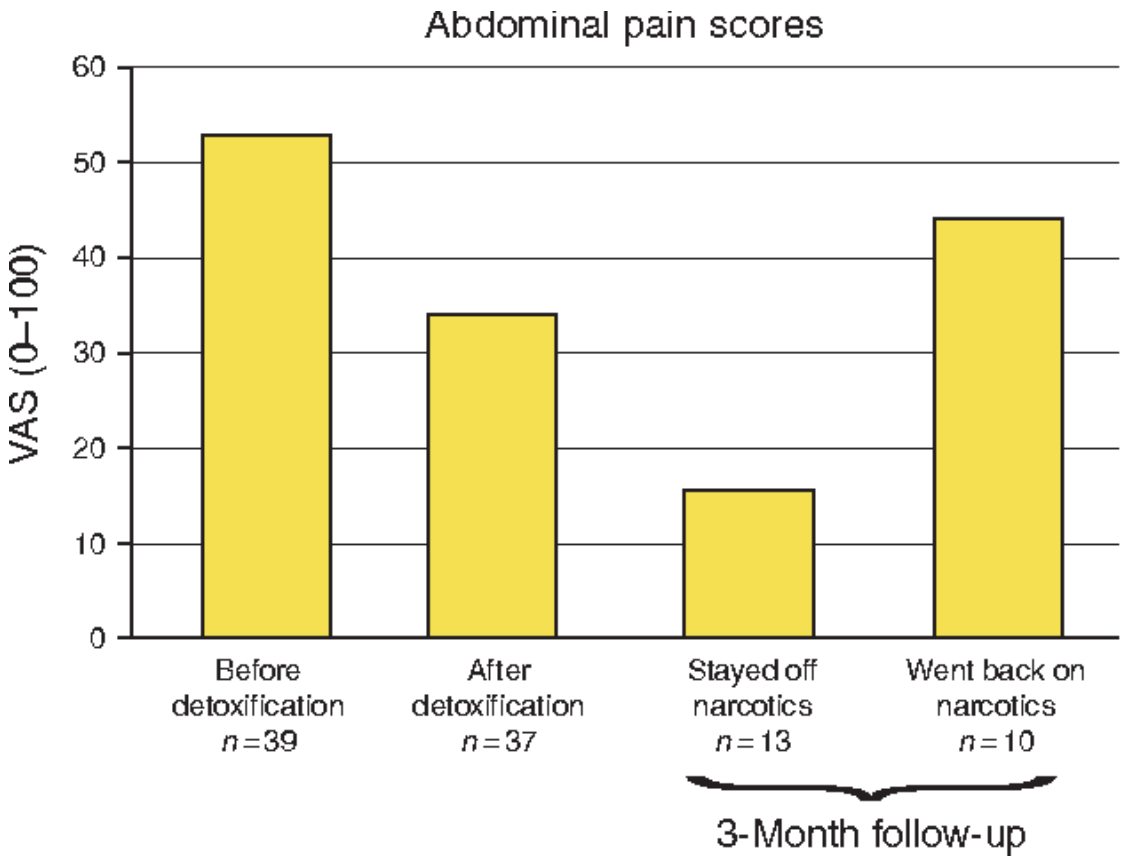
Weaning of opioid* – few days to weeks

(Clonidine – withdrawal reactions)

Psychological support

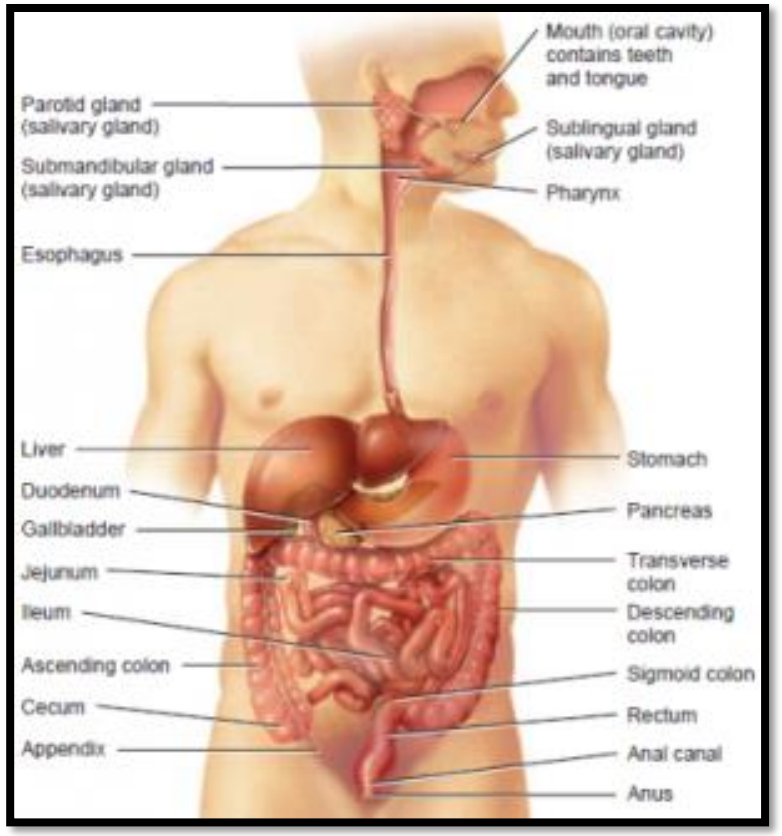
(Anxiolytics – benzodiazepines)

Narcotic bowel syndrome



Drossman et al, 2012

Opioid-induced bowel dysfunction



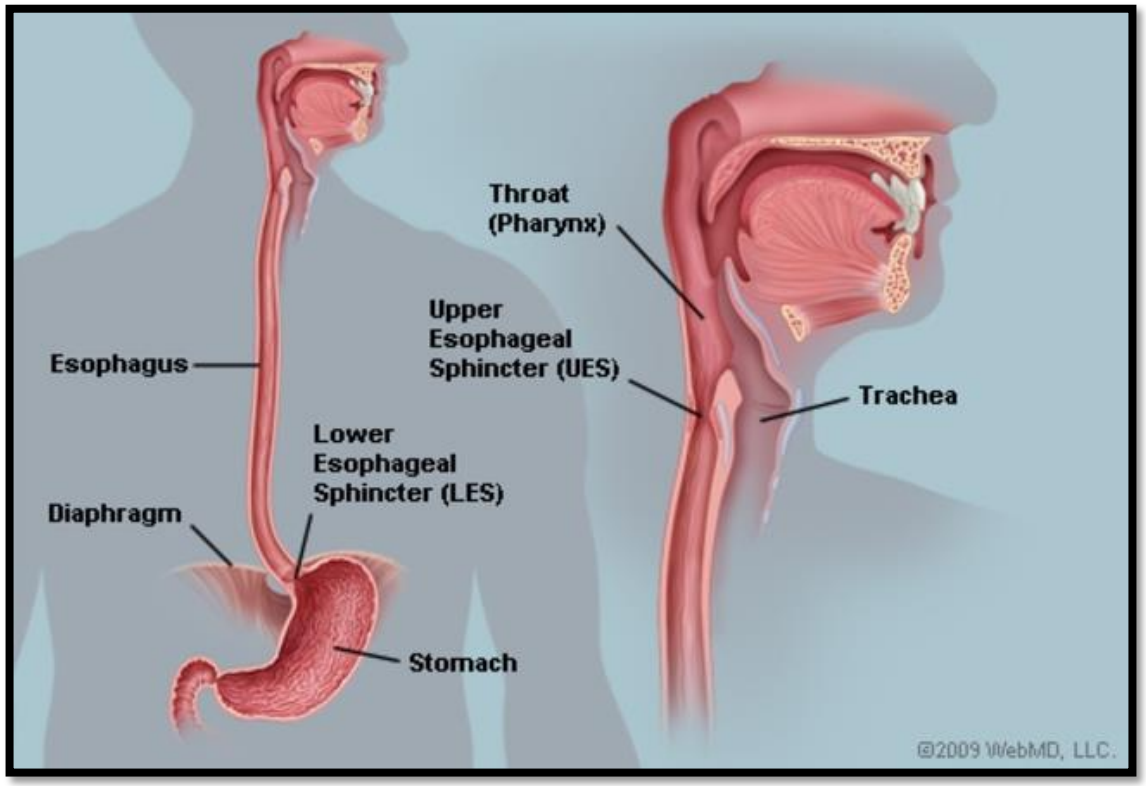
- Constipation
- Salivary gland dysfunction
- Oesophageal dysfunction
- Gastroparesis
- Sphincter of Oddi dysfunction

Salivary gland dysfunction

Salivary gland dysfunction:

- oral discomfort
- oral infections
- dental / denture problems
- oesophagitis

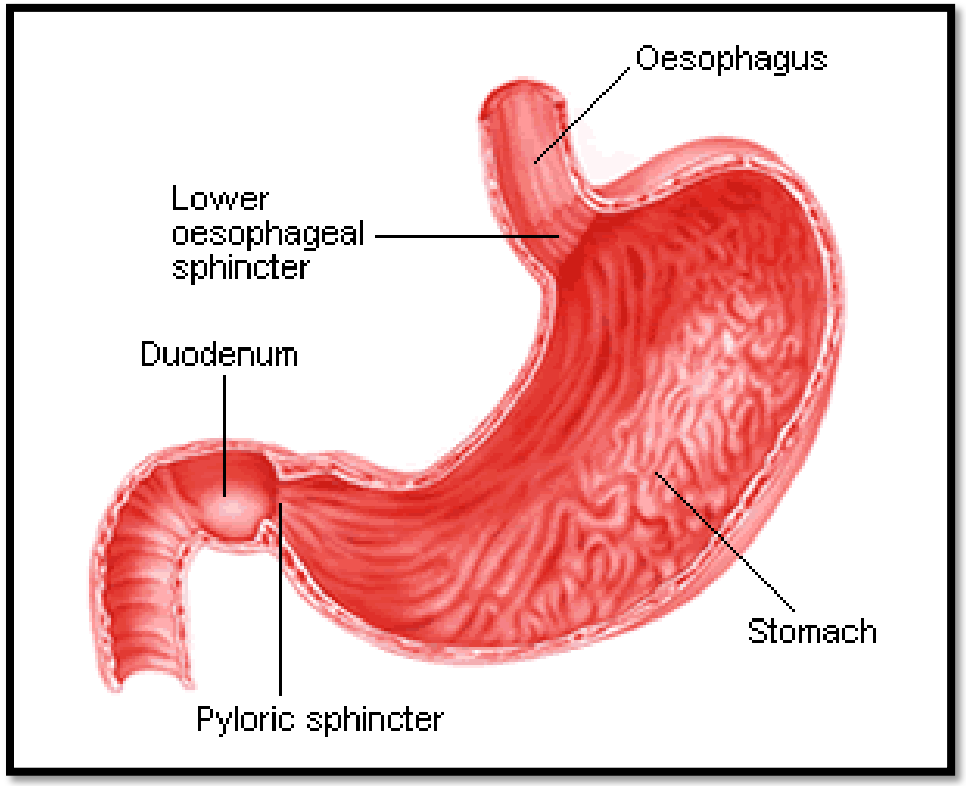
Oesophageal dysfunction



Oesophageal dysfunction:

- dysphagia (liquids)
- regurgitation
- chest pain

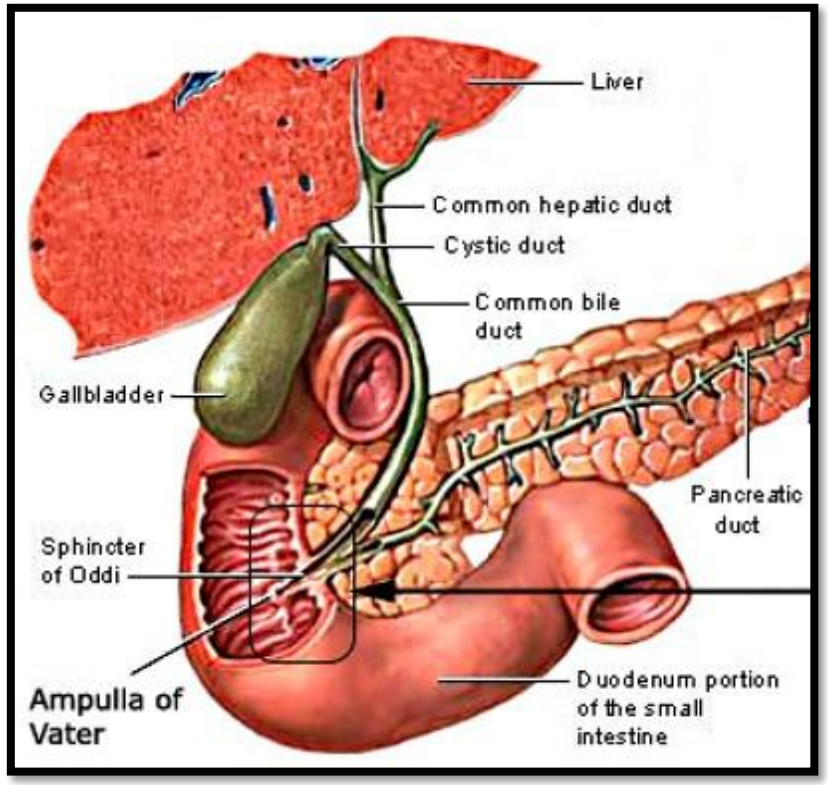
Gastroparesis



Gastroparesis:

- early satiety
- postprandial fullness
- nausea / vomiting
- bloating
- upper abdominal pain
- hiccoughs

Sphincter of Oddi dysfunction



Sphincter of Oddi dysfunction:

- biliary colic
- acute pancreatitis

“Poor man’s methadone”

Loperamide

- Normal dose (12-16mg / day)
  - peripheral mu agonist
  - poor absorption (oral bioavailability 0.3%)
  - poor penetration blood brain barrier (P-glycoprotein efflux transporter)

- Supratherapeutic doses (70-800mg / day)
  - central mu agonist
  - greater absorption
  - greater penetration blood brain barrier (P-glycoprotein efflux transporter “overwhelmed”)

Loperamide

- Researched, Abuse, Diversion and Addiction Related Surveillance (RADARS) survey
- Cross-sectional on line survey (2017)
- United Kingdom, United States of America

Webb et al, 2020

Loperamide

- UK
  - 10,019 completed surveys
  - 28.5% lifetime use of loperamide
  - 0.66% lifetime non-medical use of loperamide
  - younger age group
  - students
  - North of England
  - problematic drug users
- USA
  - 30,010 completed surveys
  - 33.7% lifetime use of loperamide
  - 5.19% lifetime non-medical use of loperamide
  - older age group
  - South of USA

Loperamide

- Reasons for non-medical use of loperamide (UK)
  - "For enjoyment / to get high" : 25.4%
  - "To come down" : 29.3%
  - "To prevent or treat withdrawal symptoms" : 22.5%

- Routes of non medical use of loperamide (UK)
  - Transmucosal : 33.0%
  - Intranasal / intrapulmonary (inhaled) : 22.6%
  - Intravenous : 21.9%
  - Other (non oral) : 13.3%

Loperamide

- “There have been reports of cardiac events including QT prolongation, torsades de pointes, and cardiac arrest in patients who have taken high or very high doses of loperamide as a drug of abuse or for self-treatment of opioid withdrawal.”

MHRA, 2017

Loperamide

- “Healthcare professionals are reminded that if symptoms of overdose occur, naloxone can be given as an antidote”

- “Since the duration of action of loperamide is longer than that of naloxone (1–3 hours), repeated treatment with naloxone might be indicated; patients should be monitored closely for at least 48 hours to detect possible CNS depression”

MHRA, 2017