Narcotic Bowel Syndrome

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Research Grant from Wyeth Pharmaceuticals:

The Narcotic Bowel Syndrome (NBS): Clinical features and prognostic factors

Adverse Effects of Opioids on the Bowel

- Opioid bowel dysfunction (OBD)
  - Constipation, nausea, vomiting, bloating, ileus, and sometimes pain
- Narcotic bowel syndrome (NBS)
  - Abdominal pain is the predominant symptom
  - Progressive and paradoxical increase in pain despite continued or escalating dosages of narcotics prescribed to relieve the pain
  - Under recognized

Pappagallo. Am J Surg 2001;182:11S–18S
Grunkenmeier et al. Clin Gastro Hep 2007;5:1126-1139
Mehendale, Yuan. Dig Dis 2006;24:105–112

Narcotic Bowel Syndrome

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:1126–1139

REVIEW

The Narcotic Bowel Syndrome: Clinical Features, Pathophysiology, and Management

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See CME exam on page 1122.

Narcotic bowel syndrome (NBS) is a subset of opioid bowel dysfunction that is characterized by chronic or frequently recurring abdominal pain that worsens with continued or escalating dosages of narcotics. This syndrome is underrecognized and may be becoming more prevalent. In the United States this may be the result of increases in using narcotics for chronic nonmalignant painful disorders, and the development of maladaptive therapeutic interactions around its use. NBS can occur in patients with no prior gastrointestinal disorder who receive high dosages of narcotics after surgery or acute painful problems, and among patients with functional gastrointestinal disorders or other chronic gastrointestinal diseases who are managed by physicians who are unaware of the hyperalgesic effects of chronic opioids. The evidence for the enhanced pain perception is based on the following: (1) activation of excitatory antianalgesic pathways within a bimodal opioid regulation system; (2) descending facilitation via dynorphin rostral ventral medulla and pain facilitation via pronociceptin and cholecystokinin activation, and (3) glial cell activation that produces morphine tolerance and enhances opioid-induced pain. Treatment involves early recognition of the syndrome, an effective physician–patient relationship, graded withdrawal of the narcotic according to a specified withdrawal program, and the institution of medications to reduce withdrawal effects.

It has long been recognized that opiates can adversely affect gastrointestinal motility. These effects, known as opioid bowel (or gastrointestinal) dysfunction, are manifest as constipation, nausea, bloating, ileus, and sometimes pain.[1–3] When pain is the predominant symptom, the condition has been termed *narcotic bowel syndrome* (NBS). NBS is characterized by the progressive and paradoxic increase in abdominal pain despite continued or escalating dosages of narcotics prescribed in an effort to relieve the pain. This entity[4–6] first was reported 2 decades ago in the United States and 10 years ago in China.[7] At the University of North Carolina (UNC) Center for Functional Gastrointestinal (GI) and Motility Disorders (www.med.unc.edu/ibs), patients frequently are seen with chronic and refractory gastrointestinal disorders. Many of these patients are experiencing NBS and benefit from narcotic detoxification.

In this narrative review we discuss our experience with the clinical features of this syndrome; discuss the changing practice of narcotic usage for functional GI pain, which may make NBS more common; review new information on the possible neurophysiologic determinants of the syndrome; offer diagnostic criteria; and recommend an approach to management of patients with NBS. We performed a Medline search and could identify only 4 case reports on this topic, spanning more than 20 years. Accordingly, there is a limited and fragmented evidence base and the references provide supportive evidence for the statements made based on clinical experience. Nevertheless, we consider this to be a rapidly emerging clinical issue that requires attention. We propose that if the physician recognizes the many facets of NBS with proper diagnosis and management, the clinical outcome can improve greatly and health care costs may be reduced.

Diagnosis

The syndrome is characterized by chronic or intermittent colicky abdominal pain that worsens when the narcotic effect wears down. Although narcotics may seem helpful at first, over time the pain-free periods become shorter and tachyphylaxis occurs, leading to increasing narcotic doses. Ultimately, increasing dosages enhance the adverse effects on pain sensation and delayed motility, thereby initiating the development of NBS.

Although pain is the dominant feature, nausea, bloating, intermittent vomiting, abdominal distension, and constipation are common. Eating can aggravate the symptoms, so when the condition lasts for weeks, mild weight loss may occur because of anorexia, or a willful restriction of eating out of fear of aggravating the pain (sitophobia). The symptoms may correlate with delayed gastric emptying and intestinal transit.

A common and misleading consequence of NBS is that abdominal radiographs may show signs suggestive of a partial intestinal obstruction, which in fact is caused by an adynamic ileus or pseudo-obstruction. There also may be large amounts

Abbreviations used in this paper: FGID, functional gastrointestinal disorders; GI, gastrointestinal; IBS, irritable bowel syndrome; IV, intravenous; NBS, narcotic bowel syndrome; RVM, rostral ventral medulla; UNC, University of North Carolina.

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Grunkemeier, DMS et al., Clin Gastroenterology and Hepatology 2007; 5:1126

Typical Clinical Presentation for NBS

- Patient presents with chronic or recurrent abdominal pain which is treated with narcotics
- Narcotics may have relieved pain initially but then tachyphylaxis occurs
- Pain worsens when the narcotic effect wears off
- Shorter pain-free periods result in increasing narcotic doses
- Increasing doses further alter motility and aggravate pain
- Can occur with in patients FGID, organic disease or otherwise health subjects (e.g., post operative)

Grunkenmeier et al. Clin Gastro Hep 2007; 5:1126

Case 1: NBD Developing in FBD

- 42 yo woman with h/o IBS for > 20yrs but **worsening lower abdominal pain x 3 yrs**
- PCP was prescribing oxycodone (10 mg tid) for pain and clonazepam and paroxetine for anxiety and depression
- Pain seemed different from her more typical IBS symptoms: **more persistent and not relieved by defecation**
- Pain associated with abdominal bloating, nausea, vomiting, and depressive symptoms
- Twice **tried to stop narcotics but was unsuccessful due to increasing pain**
- Was placed on outpatient detoxification and 1 year later she remained off narcotics with only mild IBS symptoms

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Functional Pain Disorders Particularly Vulnerable to Being Treated with Narcotics

- Abdominal pain is a key feature and associated with:
  - Pain is a strong predictor of health care seeking
  - 43% of patients admitted for abdominal pain are discharged from hospitals with no specific explanation for their pain
- Perception of no other treatment options
- Narcotics are more likely prescribed when symptoms are severe and patient demands pain relief

Spiegel et al. Arch Intern Med 2004;164:1773-1780
Lembo A et al. CGH 2005;3:717–725
Grunkemeier D.M.S. et al. CGH 2007, 5:1126
Gray DW et al. Br J Surg 1987;74:239–242

Case 2: NBS with Crohn's Disease

- 20 y/o woman with a 16 mo h/o narcotic use (methadone 260 mg/d) for low back pain
- Admitted with obstipation; methadone tapered to 230 mg/d and enemas given
- 3 days later, patient returned with N/V, RLQ pain
- Studies:
  - CT scan: short segment of TI thickening and retained fecal material
  - Colonoscopy: congested TI without obstruction; biopsies showed mild chronic active ileitis
  - SBFT:20 cm of thickened, non-obstructing TI

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Case 2: NBD with Crohn's Disease

- Narcotics reinstituted for pain presumed due to Crohn's disease and pain got worse
- The GI service was consulted and determined that although the patient had Crohn's disease, the pain pattern was related clinically to NBS
- Corticosteroids and 5-ASA were started and methadone was tapered gradually over 11 days
- Pain improved with withdrawal of narcotics
- Patient continued to use narcotics → worsening pain that improved with withdrawal of narcotics (unrelated to CD activity)

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NBS Can Occur in Organic GI disorders

- The pain is attributed to an underlying disease
- The physician feels justified to use narcotics even when disease activity is not sufficient to explain pain
- Assessment of disease activity relative to the patient's pain behavior is needed

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Case 3: NBD Developing Postoperatively

- 40 yo lawyer admitted with severe abdominal pain, n/v fever
- No history of previous GI symptoms
- Severe RLQ tenderness and leukocytosis → surgery → normal
- Postoperatively given 40 mg/day of IV Morphine Sulphate
- 2 weeks later increasing pain and obstipation; x-ray showed partial small bowel obstruction → 2nd surgery
- 6 cm. small bowel resected due to adhesions and SBO
- 1 wk later → peritonitis from anastamotic perforation → 3rd surgery
- Continued in hospital for 2 months on 40 → 60 → 80 mg/day IV morphine sulfate for severe pain n/v with “pseudo-obstruction”
- GI consult diagnosed NBS and patient detoxified over 6 days
- Patient discharged → continued abdominal pain, bloating for 1yr
- No difficulties over subsequent 10 years

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NBS Can Occur in Otherwise Healthy Persons

- Can occur postoperatively from high dosages of IV narcotics
- Narcotics are justified because the pain and N/V is attributed to surgical injury and postoperative ileus
- Surgery → visceral hypersensitivity → enhanced pain
- Increased narcotics → ileus → pseudoobstruction
- NBS develops

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Challenges for Physicians

- Physicians are ambivalent about prescribing narcotics for non-malignant chronic pain
- Patient's requests for pain relief → difficult dialog about narcotic use. This can interfere with discussion of other treatment options
- The physician may then feel unwilling or unable to manage the clinical condition → negative interaction
- Patient may feel hopeless and angry at the physician when the request for narcotics is rejected

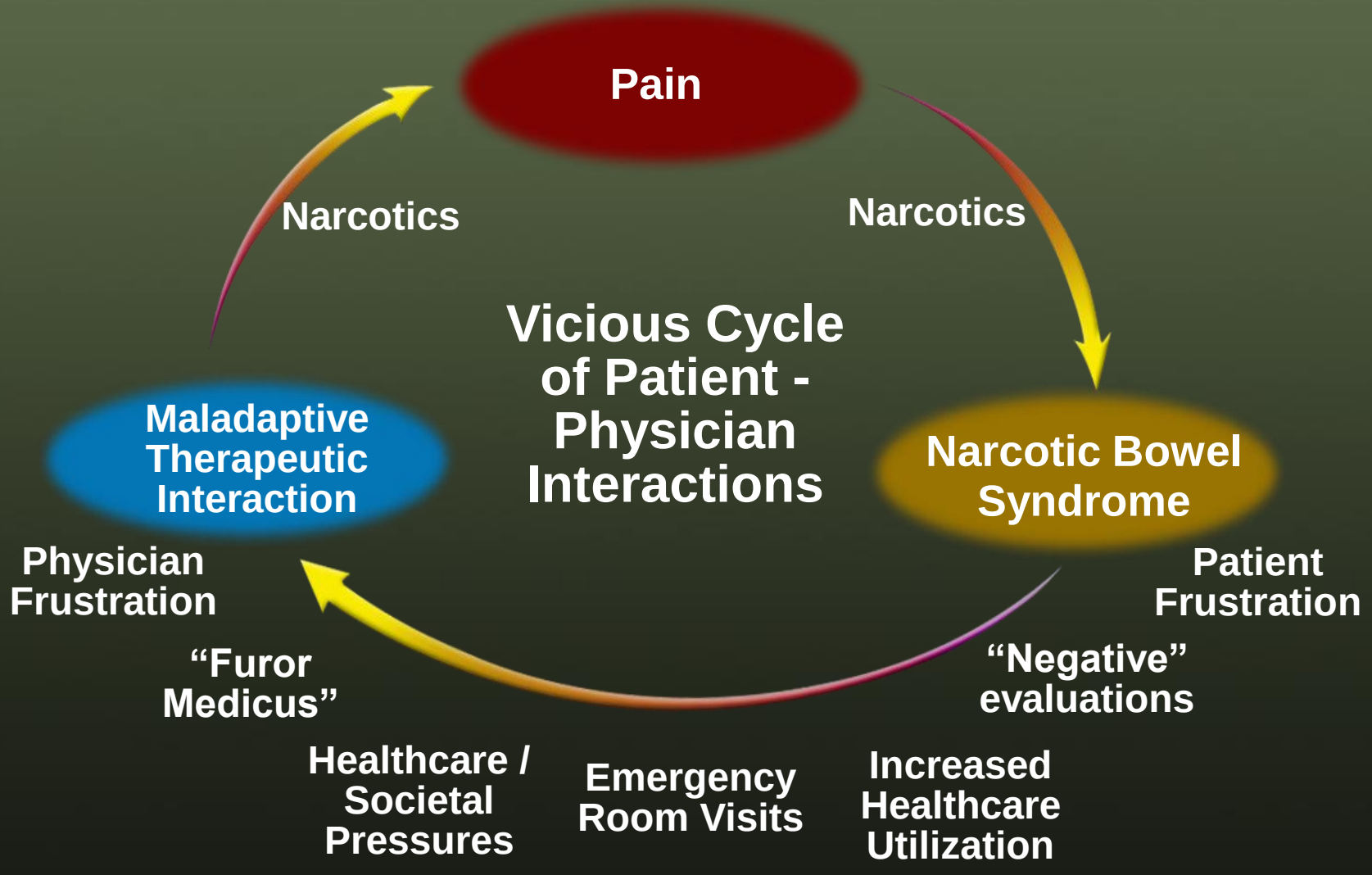
Grunkemeier D.M.S. et al. Clin Gastro and Hepatology 2007; 5:1126
Drossman DA. Am J Gastroenterol 1997; 92:1418

Challenges for Physicians (cont.)

- Nonverbal communication of pain most predictive of narcotic prescribing
- Time constraints for clinical visit increases diagnostic testing → reduces effective communication and information gathering → improper-decision making
- Patients may be discharged from ER or released from clinic with narcotic Rx for pain without a diagnosis or treatment plan or follow-up
- PCP must deal with lack of diagnosis and pressure to prescribe narcotics

Turk DC et al. Clin J Pain 1997; 13:330
Drossman DA. Gastroenterology 2004; 126:952

Narcotic Bowel Syndrome



Narcotic Prescribing in the Health Care Setting

- The USA (4.6% of world population) prescribes 80% of world's opioids.
- 1997 → 2002: 700-1200% increase in retail sales of oxycodone and methadone
- 1993 → 1999: 100% increase in hydrocodone associated ED visits
- Prescribing has shifted from acute severe pain or palliative care of malignancies to prolonged use in chronic nonmalignant pain (e.g. IBD, FGIDs)
- Pain treatment centers shifted to narcotic treatments for non-malignant pain → emphasizes "quick fix" over multidisciplinary pain treatment
- There is no scientific evidence for long-term benefit of narcotics in non-malignant pain
- Greater sensitivity of bowel in FGIDs → more side effects from narcotics
- These changing practice patterns are enabled by 3rd party payers due to greater cost benefit with shorter visits and expensive delivery systems
- The net effect is increased annual health care expenditures

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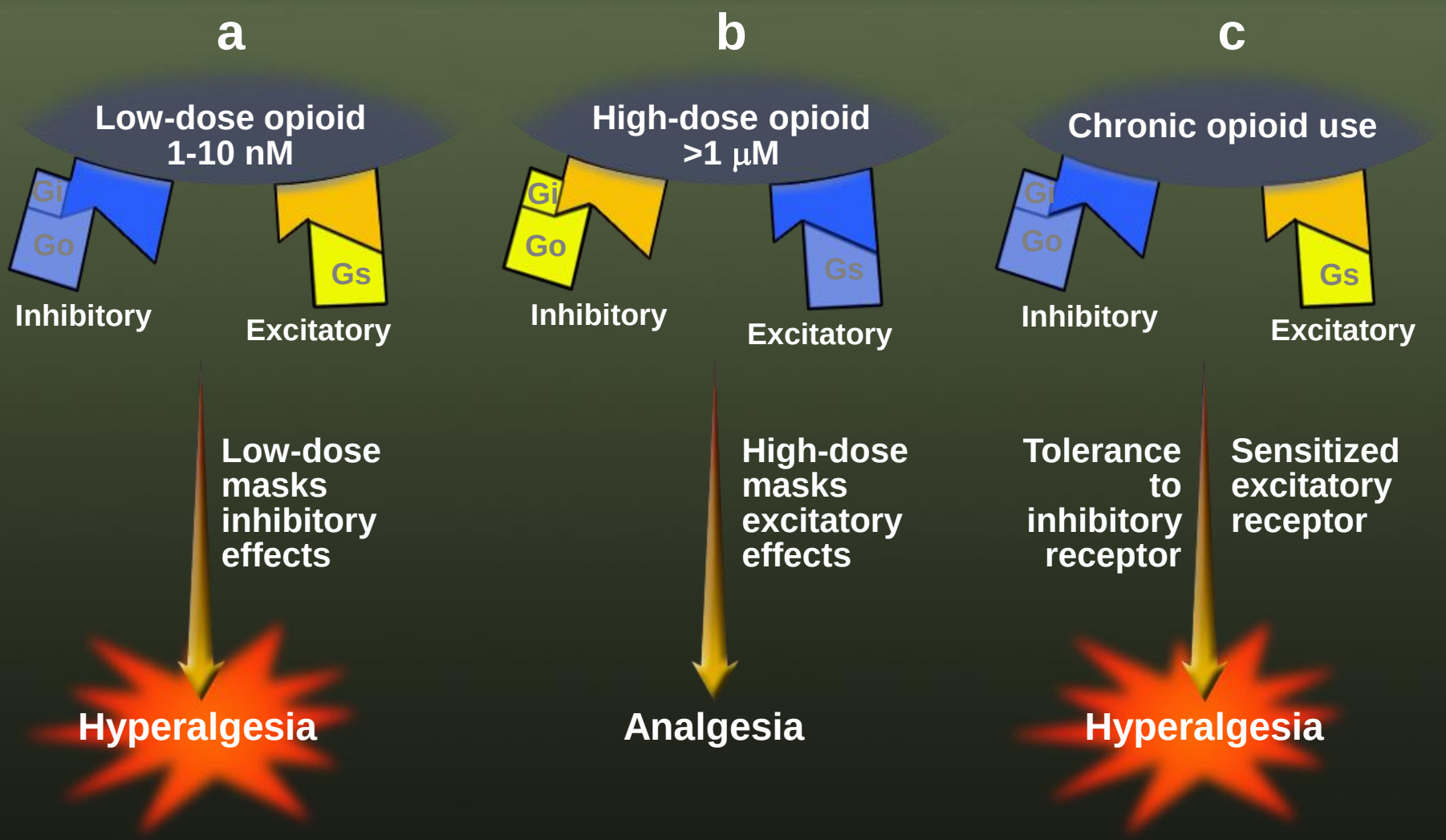
Retail Sales of Opioid Medications 1997-2006

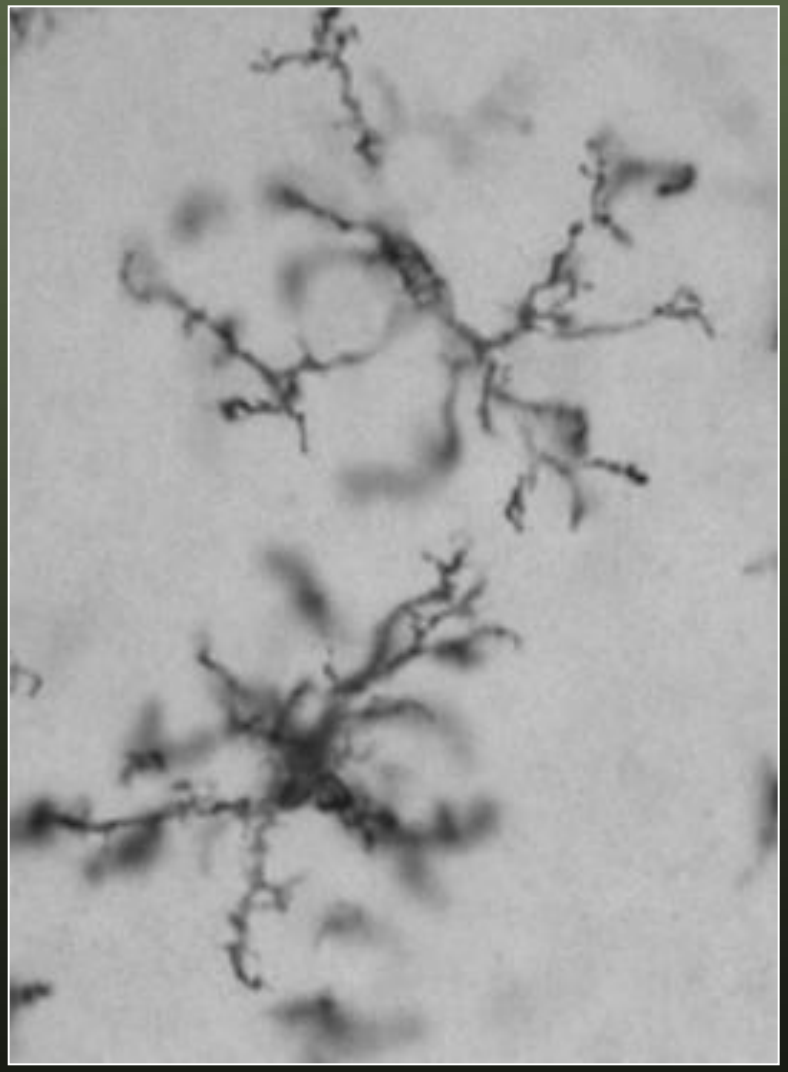
	1997	2006	% change
Morphine	5,922,872	17,507,148	195.6
Hydrocodone	8,669,311	29,856,368	244.4
Oxycodone	4,449,562	37,033,986	732.3
Methadone	518,737	6,621,687	1176.5

ARCOS: Automation of Reports and Consolidated Orders System. http://www.deadiversion.usdoj.gov/arcos/index.html (accessed June 22, 2009)
Hall et al. JAMA. 2008 Dec; 300(22):2613-2620

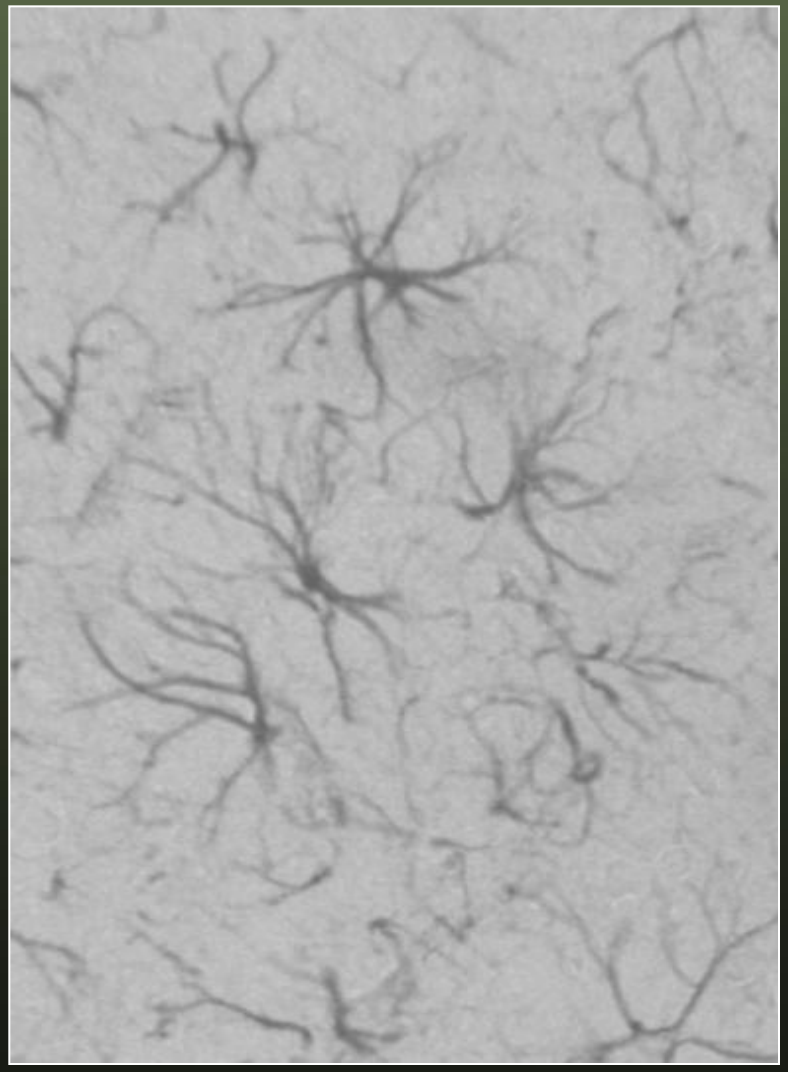

a
Low-dose opioid
1-10 nM
Gi
Go
Gs
Inhibitory
Excitatory
Low-dose masks inhibitory effects
Hyperalgesia
b
High-dose opioid
>1 μM
Gi
Go
Gs
Inhibitory
Excitatory
High-dose masks excitatory effects
Analgesia
c
Chronic opioid use
Gi
Go
Gs
Inhibitory
Excitatory
Tolerance to inhibitory receptor
Sensitized excitatory receptor
Hyperalgesia

Glia of Brain and Spinal Cord

Microglia



Astrocytes



Potential Physiological Mechanisms for NBS

- Bimodal (Excitatory/Inhibitory) Opioid Modulation in Dorsal Horn
- Descending Pain Facilitation at RVM and via Dynorphin and CCK Activation
- Effects of Glial Cell Activation on Pain and Facilitation by Opioids
  - Glial cells (astrocytes and microglia) in dorsal horn can amplify pathologic pain and produce hyperalgesia
  - Infection/chronic inflammation activates glial cells → releases inflammatory cytokines → enhances neuronal excitability
  - Chronic narcotics bind to glia via μ receptors → release of proinflammatory cytokines
  - Opiates can also activate dynorphin release → glial cell activation

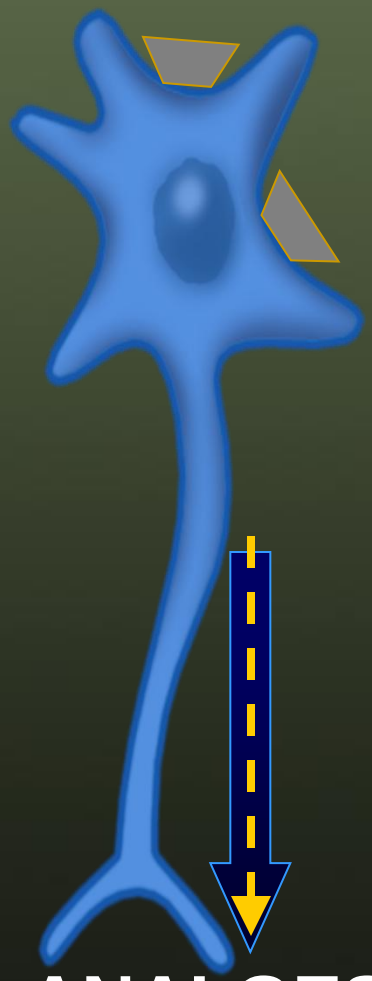
Grunkemeier D.M.S. et al. CGH 2007, 5:1126
Watkins LR et al. Trends Neurosci 2005;28:661
Hutchinson MR et al. Sci World J 2007;7:98

Effects of Opioids on Glia and Pain

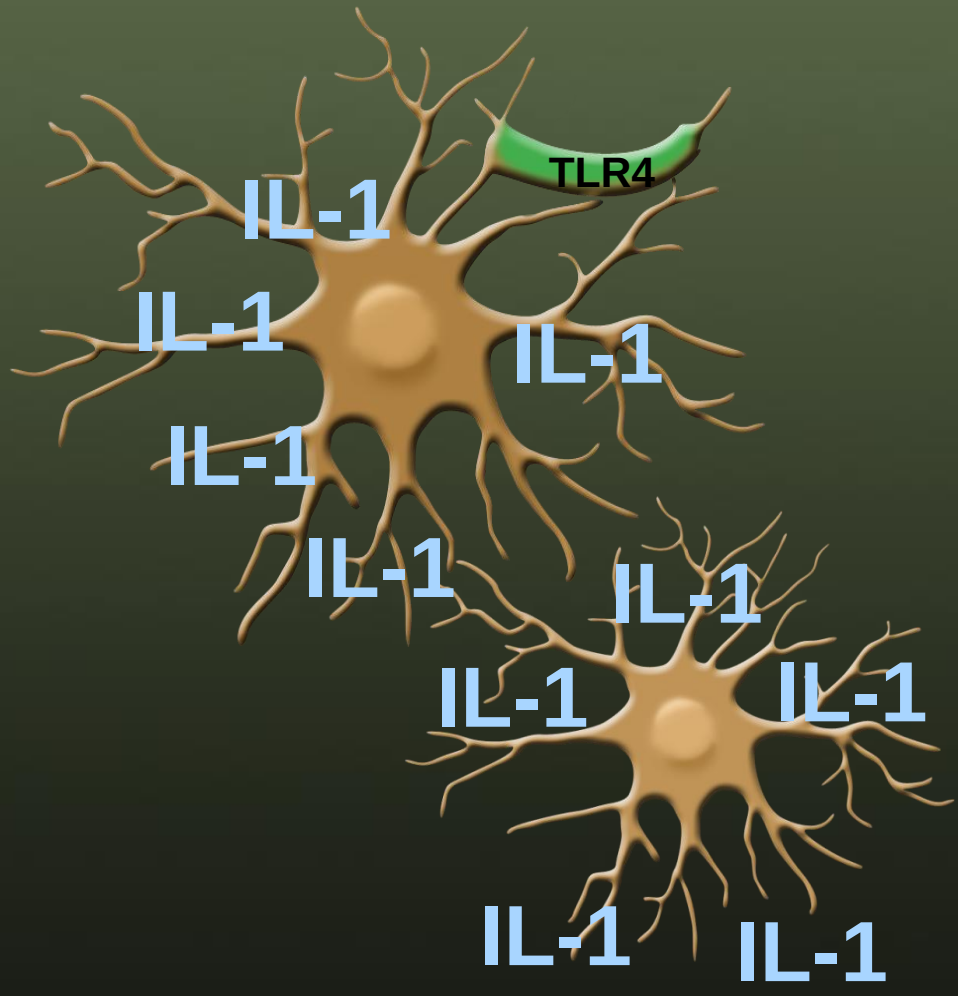
- Opioids acutely activate neuronal receptors → analgesia
- Chronic opioid use “activates” glia via toll-like receptors (TLR4, TLR2)
- TLR dependent glial activation produces pro-inflammatory cytokines (IL-1, IL-6, TNFα) and other inflammatory mediators
- Inflammatory cytokines increase neuronal excitability, produce neuropathic pain, reduce opioid analgesia and chronically, lead to opioid induced hyperalgesia.

Hutchinson M et al. Scientific World J 2007; 7:98

Opioids: Neuronal Analgesia and Glial Activation



ANALGESIA



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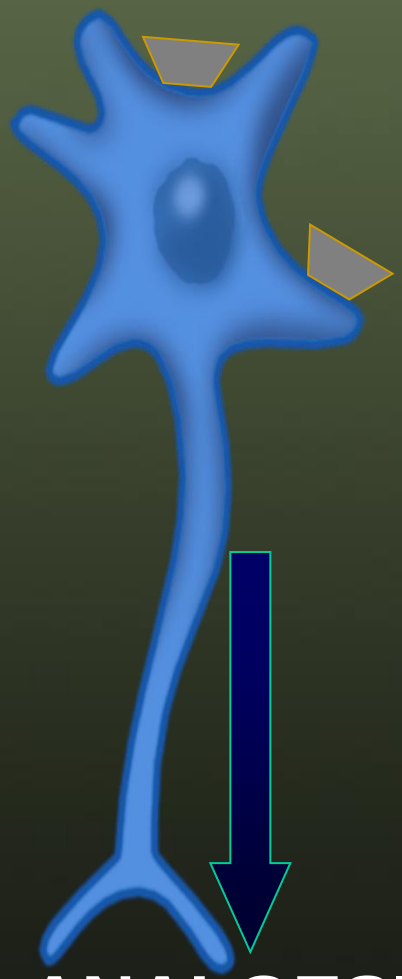
Effects of Opioids on Glia and Pain

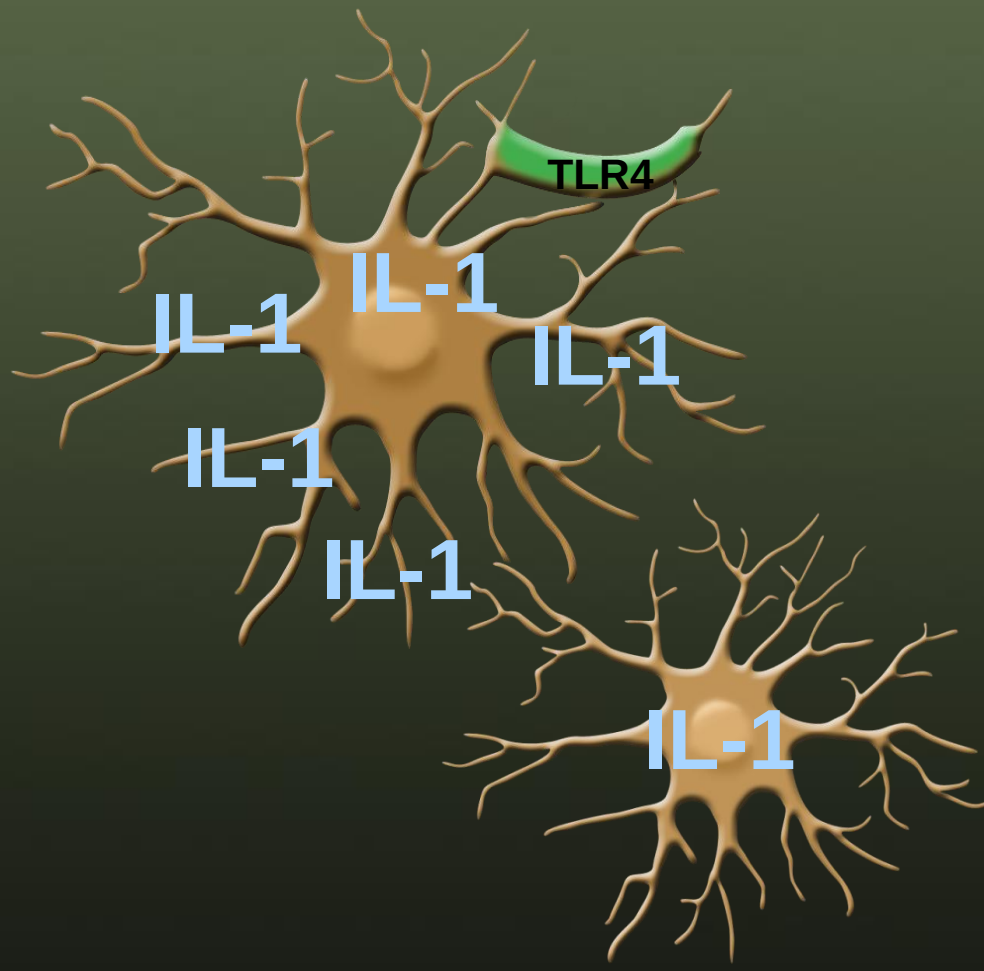
- Opioids acutely activate neuronal receptors → analgesia
- Chronic opioid use “activates” glia via toll-like receptors (TLR4, TLR2)
- TLR dependent glial activation produces pro-inflammatory cytokines (IL-1, IL-6, TNFα) and other inflammatory mediators
- Inflammatory cytokines increase neuronal excitability, produce neuropathic pain, reduce opioid analgesia and chronically, lead to opioid induced hyperalgesia.
- Low dose opioid antagonists (e.g., naloxone) can block TLR activation of glia and enhance opioid analgesia
- Future pain treatment may reduce detrimental (i.e., glial inflammatory) effects while preserving beneficial (neuronal opioid receptor analgesic) effects

Hutchinson M et al. Scientific World J 2007; 7:98

Potential Benefit of Opioid Antagonists



ANALGESIA



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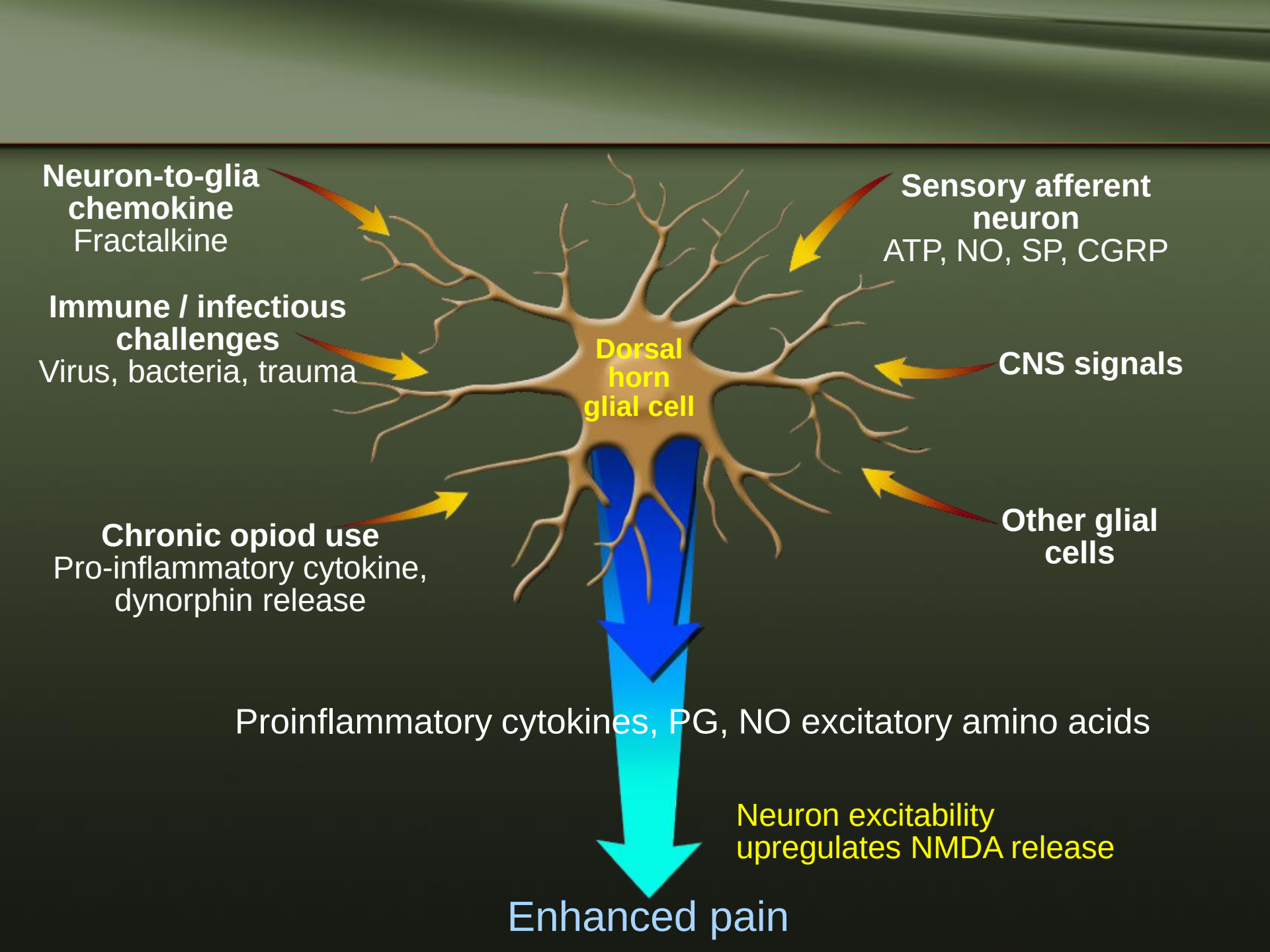

Neuron-to-glia chemokine
Fractalkine
Immune / infectious challenges
Virus, bacteria, trauma
Chronic opiod use
Pro-inflammatory cytokine, dynorphin release
Sensory afferent neuron
ATP, NO, SP, CGRP
CNS signals
Other glial cells
Dorsal horn glial cell
Proinflammatory cytokines, PG, NO excitatory amino acids
Neuron excitability upregulates NMDA release
Enhanced pain

Diagnostic Criteria: Narcotic Bowel Syndrome

Chronic or frequently recurring abdominal pain treated with acute high dose or chronic narcotics and:

- The pain worsens or incompletely resolves with continued or escalating dosages of narcotics
- There is marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstituted (“Soar and Crash”)
- There is a progression of the frequency, duration and intensity of the pain episodes
- 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., IBD, chronic pancreatitis, but the character or activity of the disease process is not sufficient to explain the pain

Grunkemeier D.M.S. et al. Clin Gastro and Hepatology 2007, 5:1126

Clinician-Patient Process and Techniques

- Physician-Patient Relationship
  - Accept the pain as real and treatable
  - Elicit the patient's concerns and expectations
  - Provide information through a dialog
  - Present the withdrawal program
  - Clinical setting
  - Gauge the patient's response

Clinician-Patient Process and Techniques

- Accept the pain as real (validate) and treatable
  - “I can see the pain has really affected your life”
  - “We can work together on this”

Clinician-Patient Process and Techniques

- Accept the pain as real and treatable
- Elicit the patient's concerns and expectations
  - "What are your biggest worries or concerns about being on narcotics (and going off narcotics)?"
  - "What do you expect will happen when you stop narcotics?"

Clinician-Patient Process and Techniques

- Accept the pain as real and treatable
- Elicit the patient's concerns and expectations
- Provide information through a *dialog:*
  - Address the patient's stated concerns and expectations
  - Provide a physiologic basis for the pain
    - "Pain in the body is experienced in the brain where it can turn 'pain volume' up or down depending on the circumstances (give examples)"
  - Discuss the effects of narcotics on pain and GI function
    - "Narcotics slow the bowels producing the constipation, bloating and vomiting you are having; they also sensitize the nerves to turn up the 'pain volume' thus making the pain worse"
  - Explain the rationale for and process of withdrawal
    - "It is likely you will be better and certainly no worse when you are off the narcotics. We will be substituting other pain control methods while we gradually taper the narcotics (so you won't be abandoned in pain)"

Clinician-Patient Process and Techniques

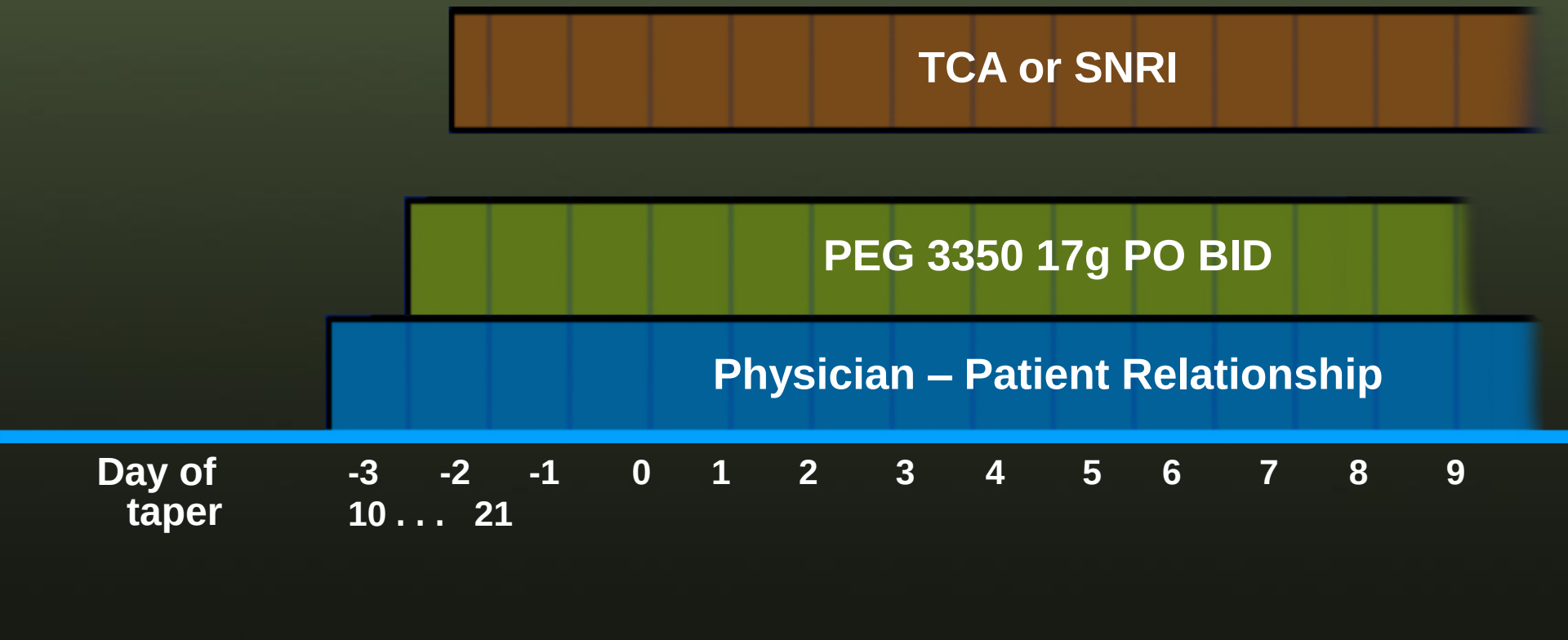
- Accept the pain as real and treatable
- Elicit the patient's concerns and expectations
- Provide information through a dialog
- Present the withdrawal program
  - Use illustrations or graphics
  - Involve a responsible family member
  - Indicate that someone will be available to address possible side effects or flare-ups

Clinician-Patient Process and Techniques

- Accept the pain as real and treatable
- Elicit the patient's concerns and expectations
- Provide information through a dialog
- Present the withdrawal program
- Clinical setting
  - Outpatient
    - Patient must be highly motivated
    - Withdrawal can take days to weeks
  - Inpatient
    - If complicated by nausea, vomiting, ileus or pseudo-obstruction
    - Limited motivation or social support
    - Requires monitoring
    - Withdrawal can occur over several days

Narcotic Withdrawal Protocol

- Accept pain as real and treatable
- Elicit patients concerns/expectations
- Provide information through a dialog
- Present the withdrawal program
- Gauge the patient's response



Antidepressants

- Tricyclics (e.g., Desipramine, Nortriptyline, Amitriptyline)
  - Pain benefit
  - Side effects (sedation, constipation) reduce adherence
  - 2^0 amines (desipramine/nortriptyline) have fewer side effects
- SNRIs (e.g., Duloxetine, Venlafaxine, Desvenlafaxine)
  - Pain benefit
  - Nausea side effects
  - Specific effects
    - Duloxetine first to be marketed for “pain with depression”
    - Venlafaxine requires higher dosage (e.g., 225 mg.) for pain
    - Benefit
- SSRIs (e.g., Paroxetine, Citalopram, Escitalopram)
  - Anxiolysis (social phobia, agoraphobia, OCD)
  - +/- pain benefit (but augments TCA effect via anxiolysis)
  - Side effects (anxiety, diarrhea)
  - Specific effects

Narcotic Withdrawal Protocol

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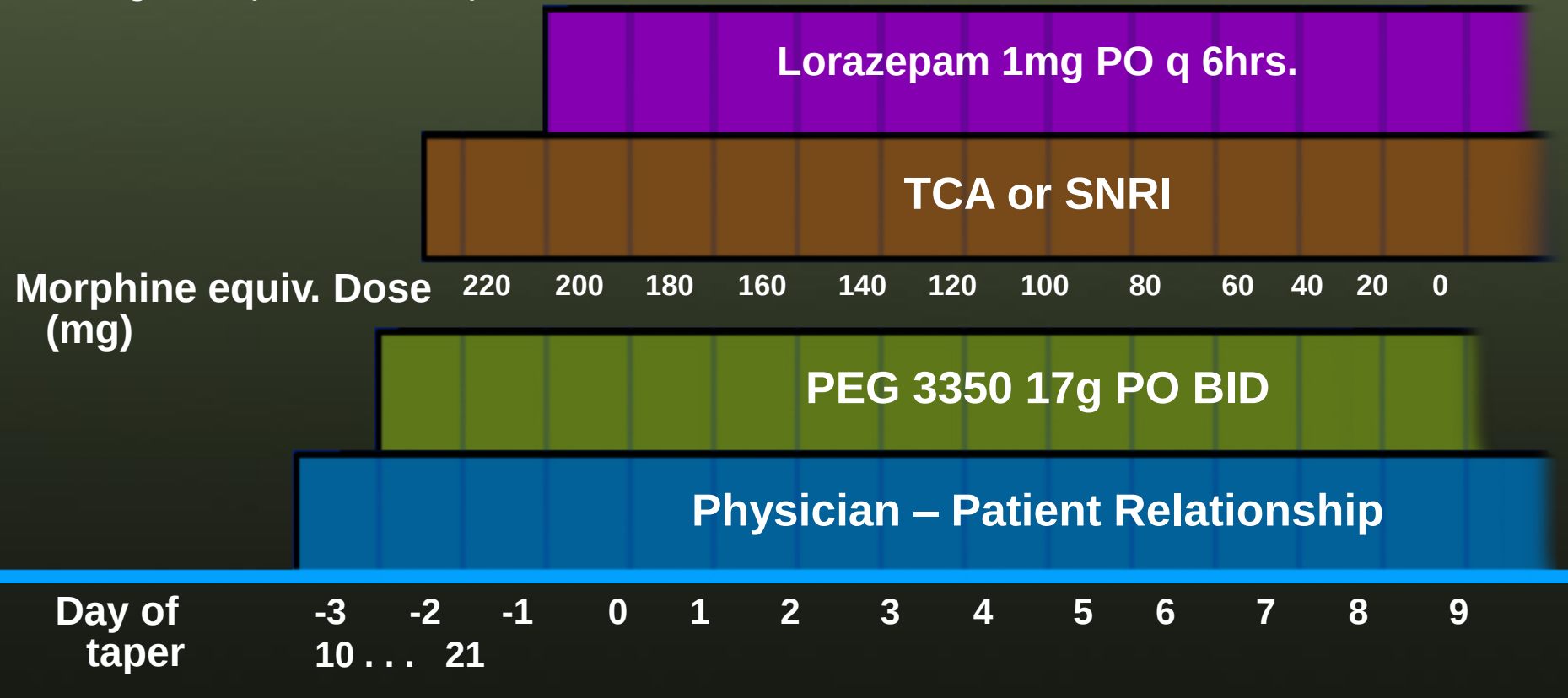

Narcotic Withdrawal Protocol

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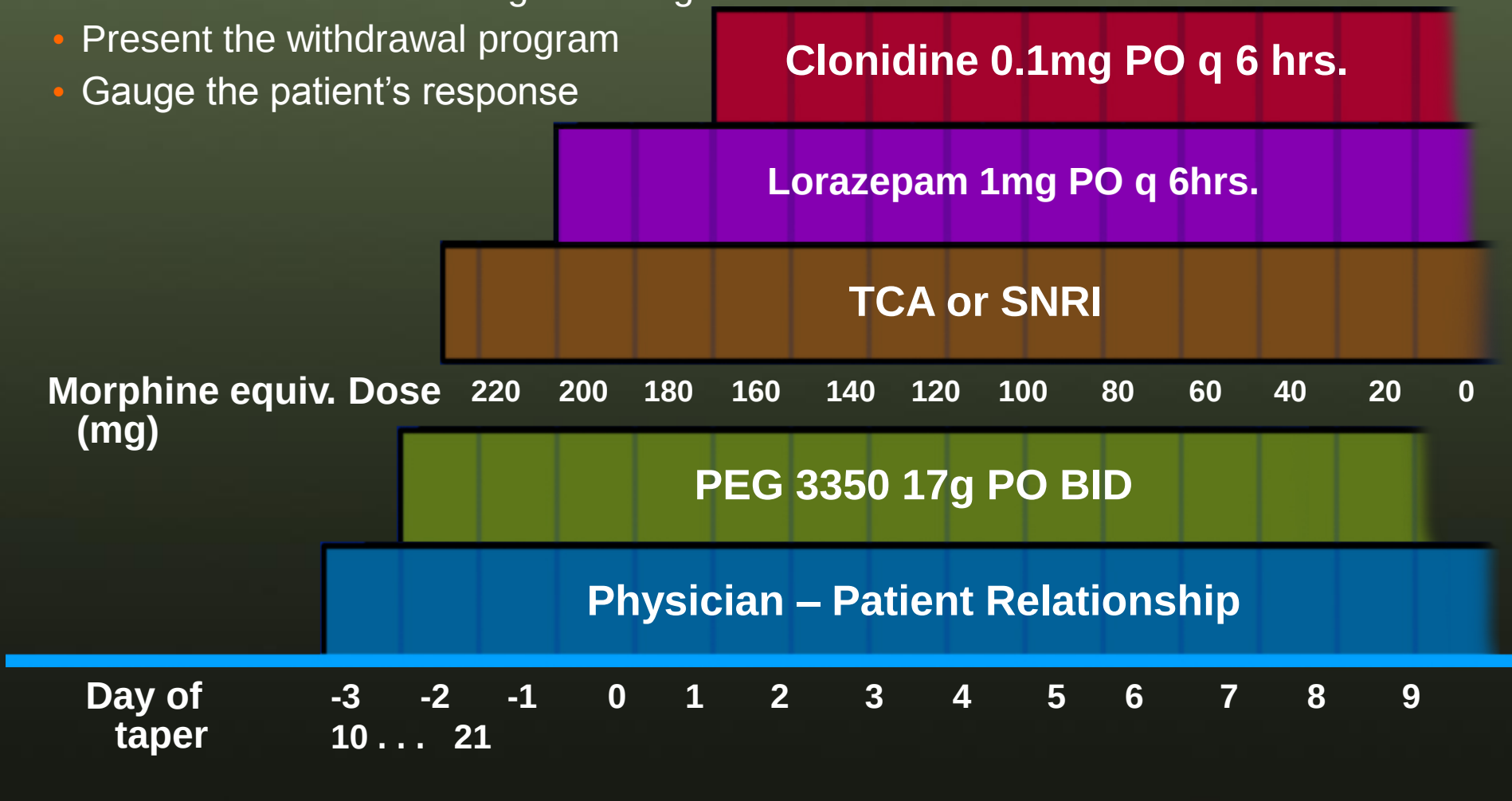

Summary – Narcotic Bowel Syndrome

- NBS is a subset of opioid bowel dysfunction
- Chronic or recurrent abdominal pain which worsens or incompletely resolves with continued or escalating dosages of narcotics
- Can occur in patients with FGID or organic diseases
- Limitations in health care: use of narcotics for non-malignant pain, poor communication, improper decision-making and lack of recognition of NBS, contribute to escalating narcotic use
- Treatment involves a protocol driven detoxification that requires a motivated patient and clinical team