Acute Postoperative Pain Management

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Why do we treat postoperative pain?

- Decrease adverse postoperative outcomes
- Quality of life
  - Return to normal daily activities.(ERAS)
- Cost of care
  - extended hospital length of stay
  - Readmissions of inpatients or unexpected admissions to hospital of outpatients (ODS)
- Patient satisfaction

Body system	Change
Cardiovascular	● Increased heart rate and blood pressure ● Increased need for oxygen ● Water retention, potential fluid overload
Respiratory	● Increased respiratory rate ● Shallow breathing ● Increased risk of infection
Immune	● Increased susceptibility to infection ● Increased or decreased sensitivity to pain ● Activation of HPA axis
Endocrine	● Increased blood glucose ● Increased cortisol production
Gastrointestinal	● Reduced gastric emptying and intestinal motility ● Nausea and vomiting ● Constipation
Urinary	● Urge to urinate/incontinence
Musculoskeletal	● Tense muscles local to injury ● Shaking or shivering ● Pilo-erection (goose bumps)
Nervous	● Changes in pain processing ● Risk of pain becoming chronic
Brain	● Anxiety/fear ● Depression ● Poor concentration ● Inhibition or promotion of pain

DB&C = deep breathing and coughing; HPA axis = hypothalamic-pituitary-adrenocort

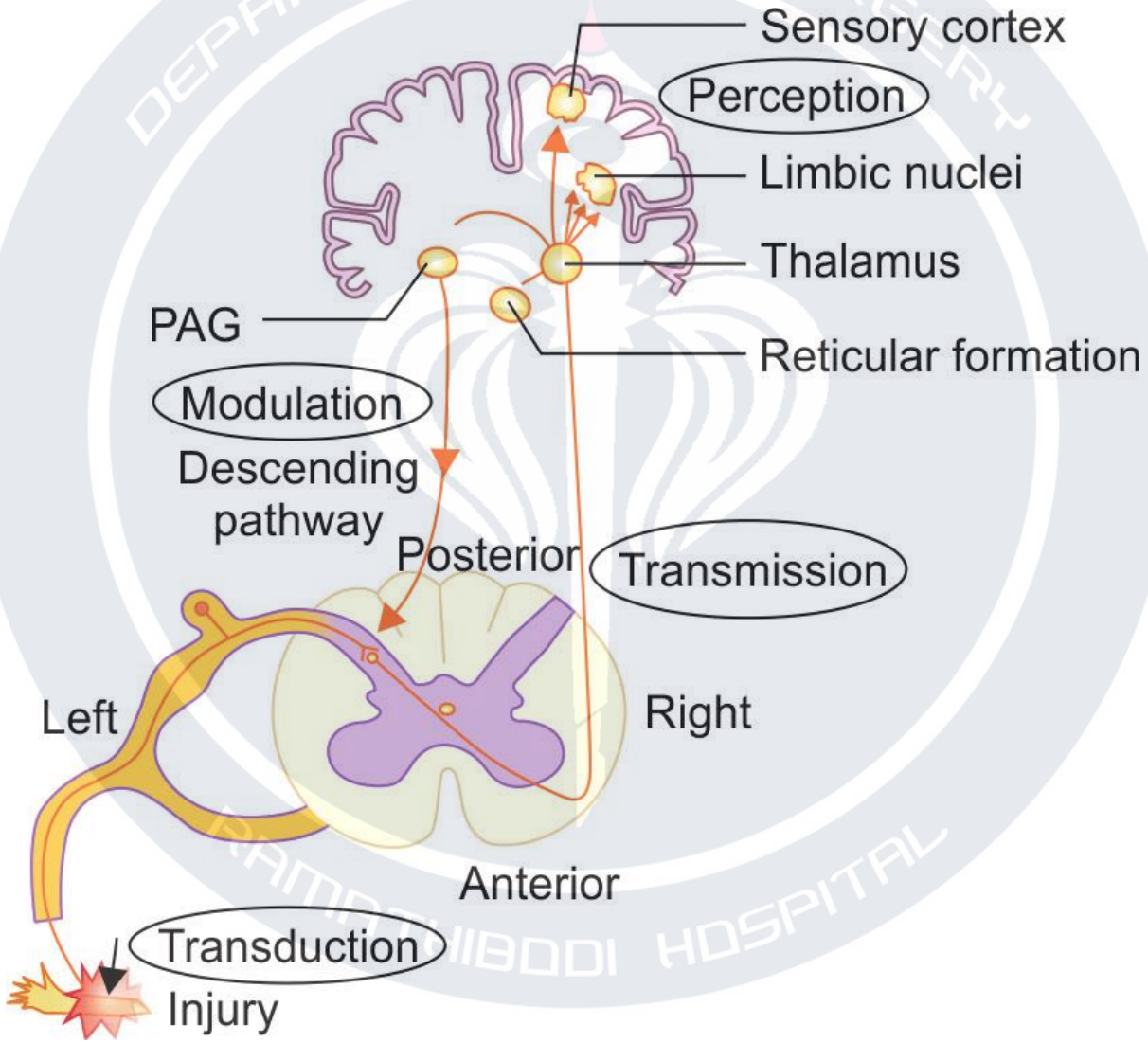
Why do we treat postoperative pain?

- Decrease persistent postoperative pain (Acute postoperative pain is a major risk factor for the development of PPP)

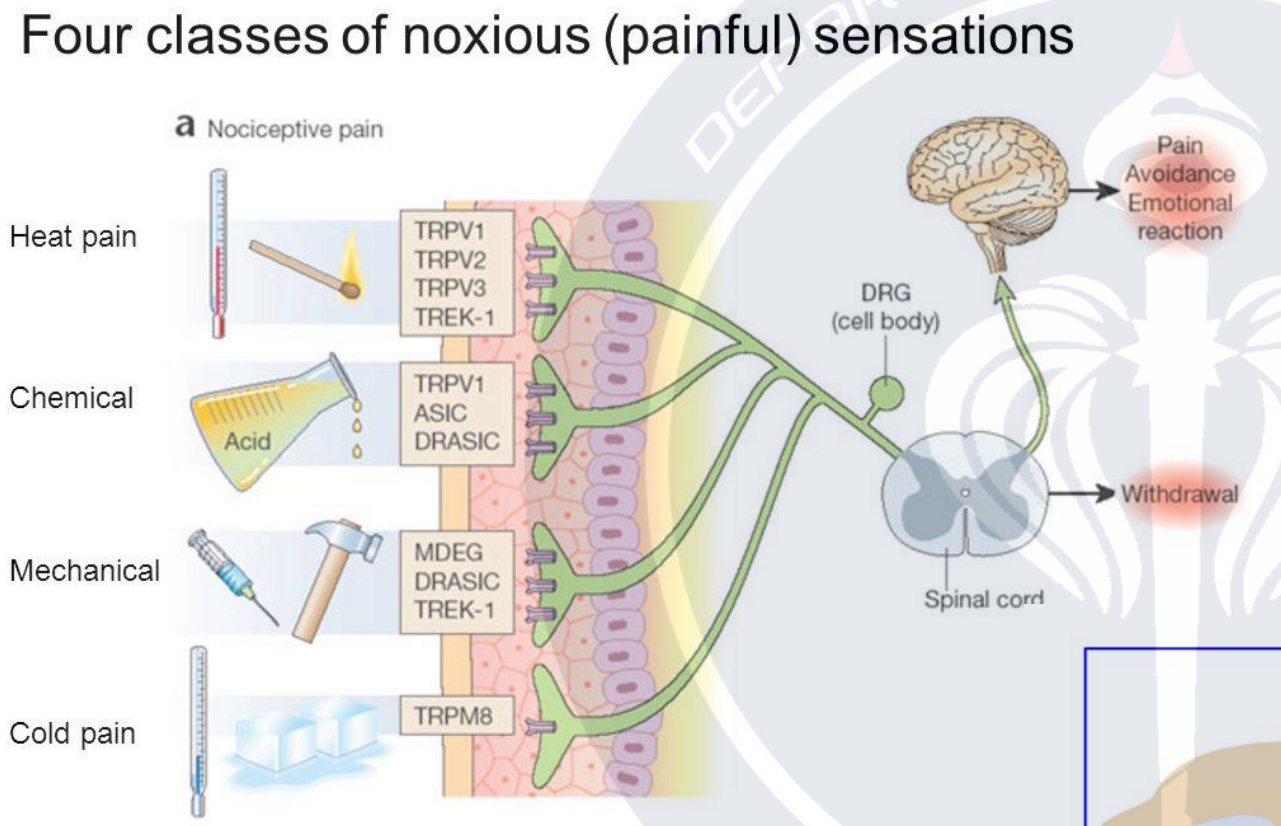
Table 1 Incidences of CPSP for different types of surgery. Data adapted from several studies.[1,3,5,6,12] Severe CPSP is defined as pain ratings of ≥5 on a scale from 0 (no pain) to 10 (worst possible pain).[1,11] CPSP, chronic post-surgical pain; NP, neuropathic pain.

Type of surgery	Incidence of all CPSP (%)	Incidence of severe CPSP (>5/10)	Chronic pain up to 12 months	Proportion of NP
Abdominal surgery (bowel and colorectal)	17–21	Not reported	Not reported	Not reported
Amputation	30–85	5–10%	75% (lower limbs)	80%
Caesarean section	6–55	5–10%	Not reported	50%
Cholecystectomy	3–56	Not reported	Not reported	Not reported
Craniotomy	7–65	25%	Not reported	Not reported
Dental surgery	5–13	Not reported	Not reported	Not reported
Hip arthroplasty	7–23	6%	28%	1–2%
Inguinal herniotomy	5–63	2–4%	30%	80%
Knee arthroplasty	13–44	15%	18%	6%
Mastectomy	11–57	5–10%	43–56% (breast cancer surgery)	65%
Sternotomy	7–50	5–10%	27%	13%
Thoracotomy	5–71	10%	41%	45%
Vasectomy	0–37	Not reported	Not reported	Not reported

Pain pathways

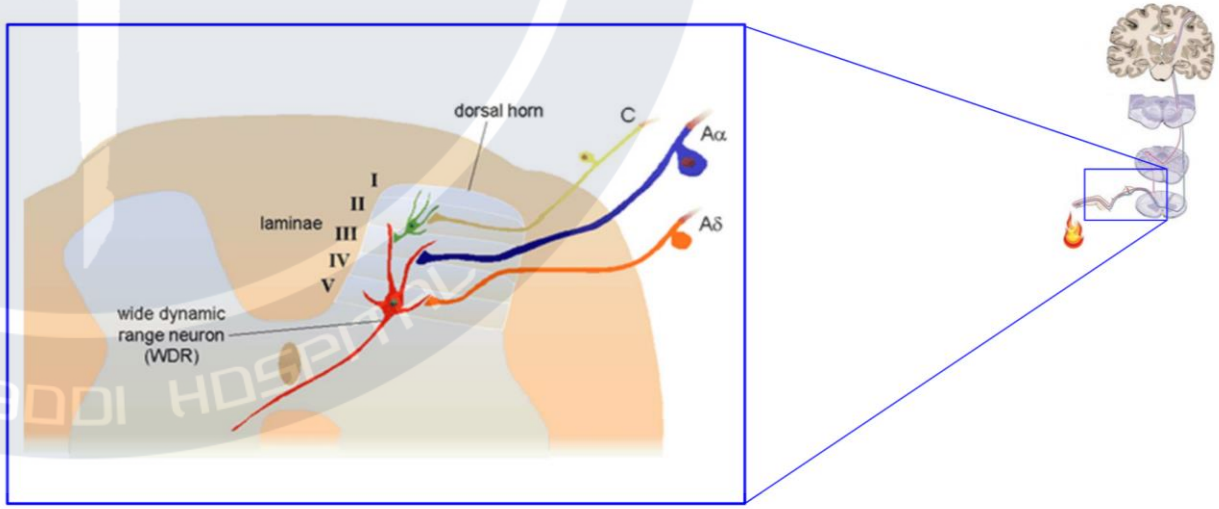


Transduction

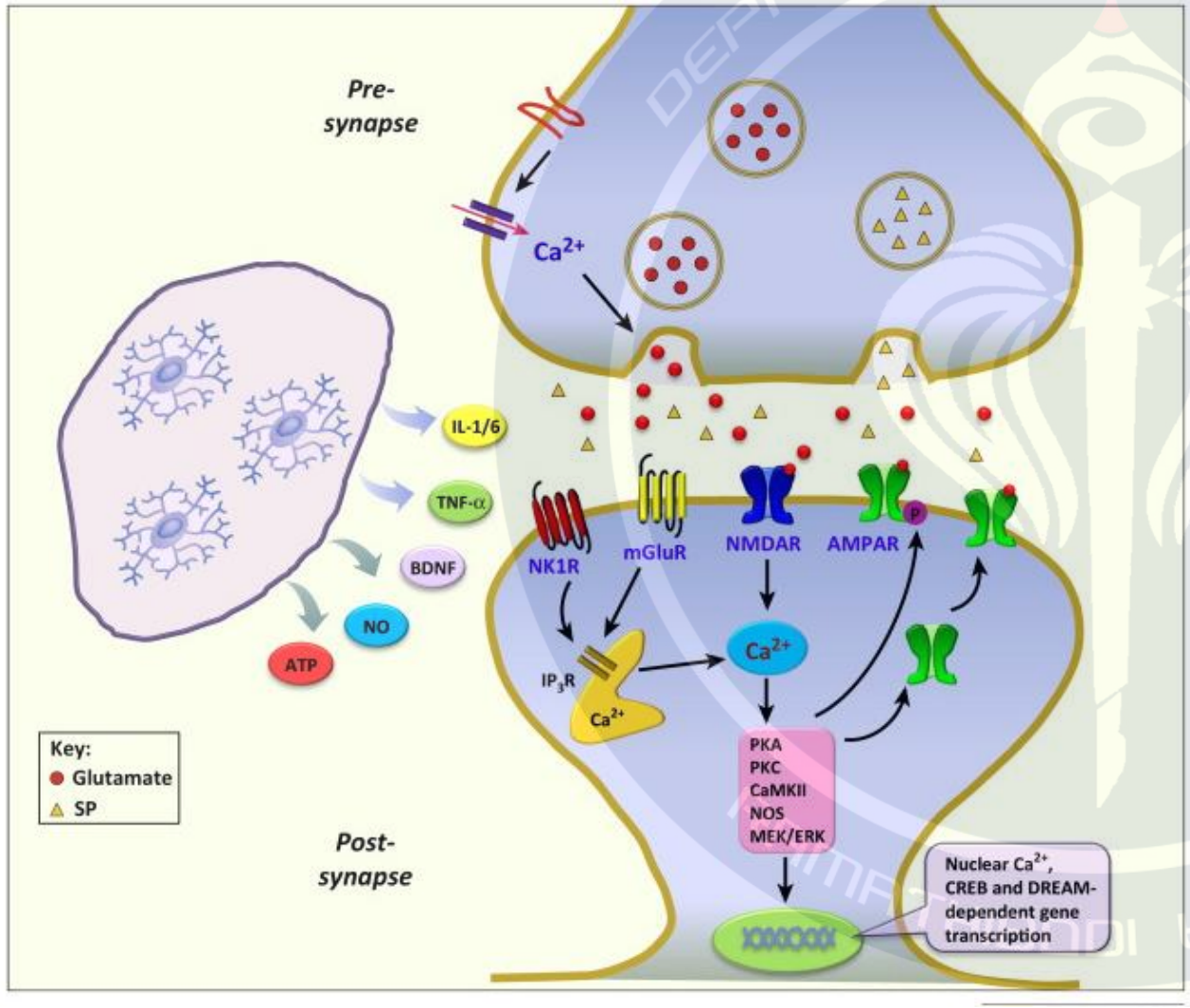


Common mediattors

Prostaglandin
K+
Lactic acid
H+
Serotonin Bradykinin
ATP
Histamime



Transmission, modulation and perception



Neurotransmitter

- Main neurotransmitter of C-fibers = substance P
- Main neurotransmitter of A-delta fibers = glutamate

Ascending tracts in spinal cord

- **Spinothalamic tract (A-delta)**

→ thalamus→somatosensory cortex →PAG in brain stem (descending inhibitory pathway)

- **Spinoreticular tract (C-fibers)**→reticular formation→thalamus and limbic system (memory and emotional components of pain)

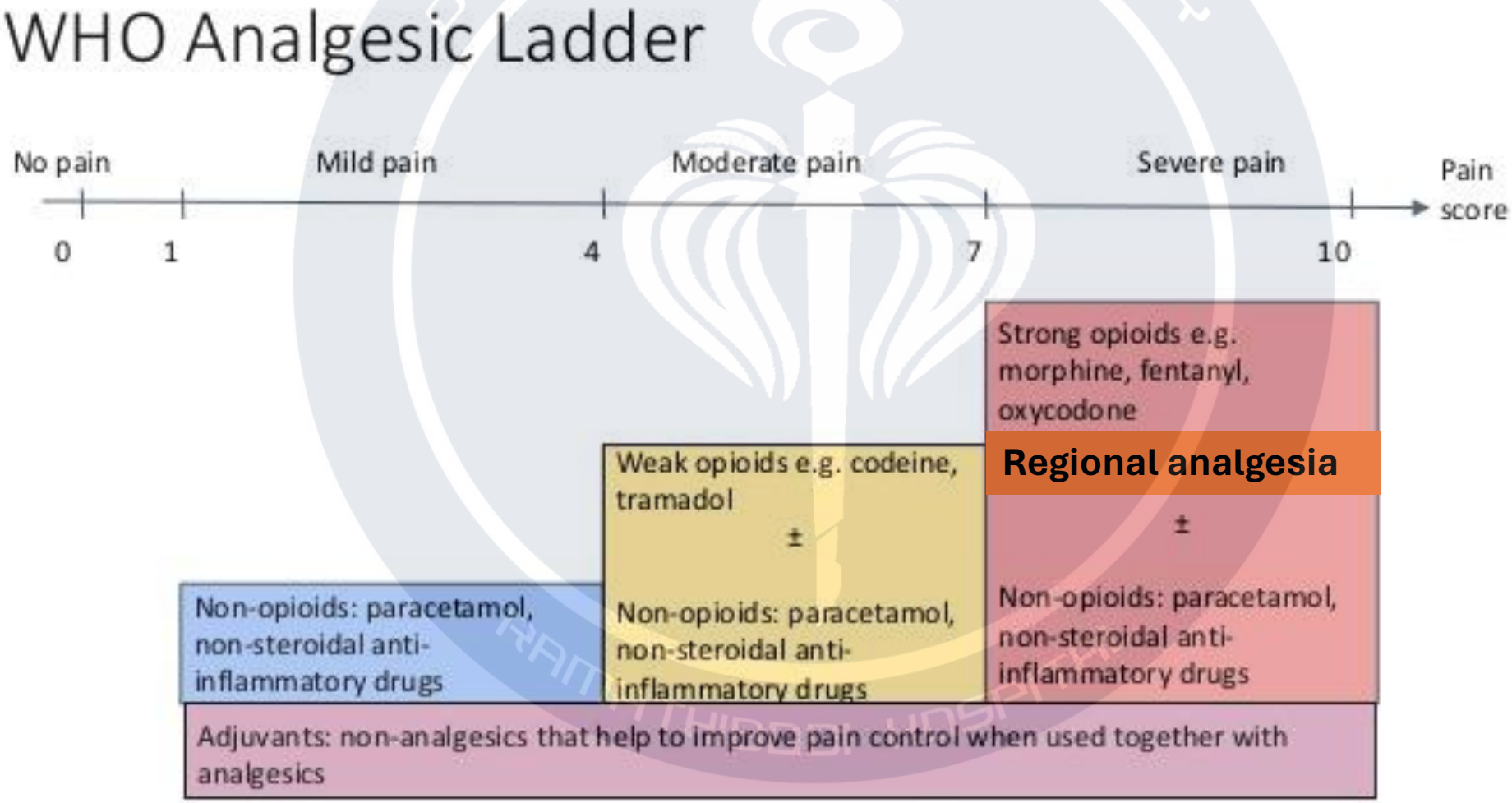
Modulation (Descending inhibitory pathway)

- Decrease production of sub P and glutamate in nerve fiber terminal synapse
- Reduce pain signal in 2nd order neuron

Concepts to improve postoperative pain management

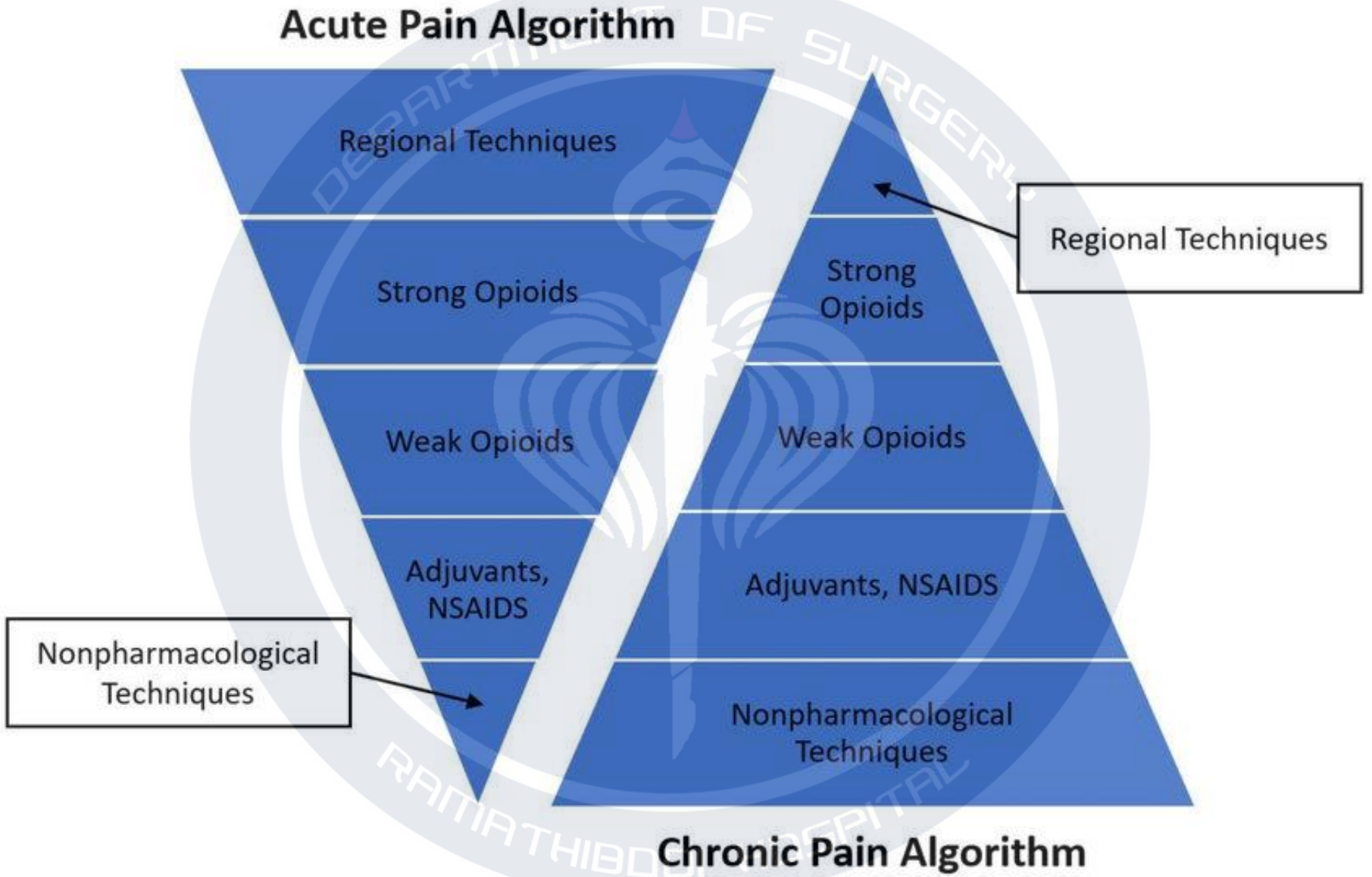
- Pre-emptive analgesia
- Preventive analgesia
  - Multimodal analgesia
    - Administration of 2 or more drugs that act by different mechanisms for providing analgesia.
    - Administered via the same route or by different routes. Thus, the
    - Aim of multimodal analgesia
      - **Improve pain relief** while **reducing opioid requirements** and opioid **related adverse effects.**
  - Proactive analgesia

Proactive analgesia



Regional anesthesia/analgesia

- Neuraxial anesthesia/analgesia
  - Spinal
    - Anesthesia
    - Analgesia ; spinal morphine
  - Epiduaral
    - Anesthesia
    - Analgesia ; LA+opioid (morphine/fentanyl)
- Peripheral nerve block
  - Targeted nerve ; femoral nerve block, sciatic nerve block
  - Interfascia plane block (analgesia, reliability?)


Acute Pain Algorithm
Regional Techniques
Strong Opioids
Weak Opioids
Adjuvants, NSAIDS
Nonpharmacological Techniques
Regional Techniques
Strong Opioids
Weak Opioids
Adjuvants, NSAIDS
Nonpharmacological Techniques
Chronic Pain Algorithm

State of the Art Safety Standards in RA

THE EUROPEAN SOCIETY OF REGIONAL ANAESTHESIA & PAIN THERAPY

prospect

procedure specific postoperative pain management

Better Postoperative Pain Management

Recommendations on this website are in the process of being updated. Please check back regularly for both updated content and new procedures

New: Open Colorectal Surgery

New: Laparoscopic Colorectal Surgery

New: Hip Fracture Repair Surgery

New: Appendicectomy

New: Cleft palate surgery

New: Sternotomy

New: Sternotomy

New: Craniotomy

Abdominal Hysterectomy 2006

Caesarean Section 2020

Complex Spine Surgery 2020

Haemorrhoidectomy 2022

Hallux Valgus Repair Surgery 2019

Inguinal Hernia Repair 2019

Laminectomy 2020

Laparoscopic Cholecystectomy 2017

Laparoscopic Hysterectomy 2018

Laparoscopic Sleeve Gastrectomy 2018

Oncological Breast Surgery 2019

Open Liver Resection 2019

Prostatectomy 2020

Rotator Cuff Repair Surgery 2019

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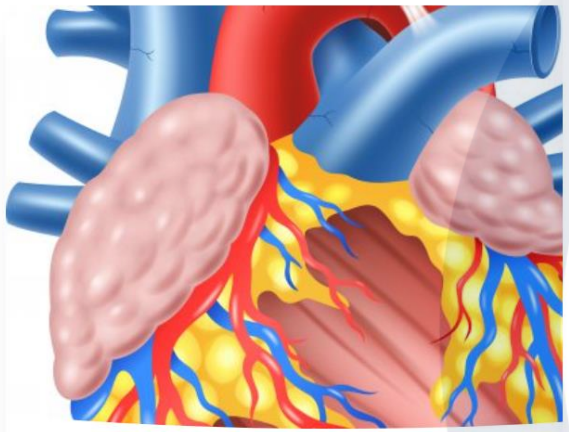


Cardiac

The ERAS Cardiac working group published its completed guideline on perioperative care after cardiac surge produced jointly with the ERAS Societ in JAMA Surg (May 2019). Portions ha been...

ERAS® Guidelines

- Anaesthesia
- Bariatric
- Breast
- Cardiac
- Colorectal
- Cytoreductive
- Emergency Laparotomy
- Gastrectomy
- Gastrointestinal
- Gynaecology
- Head & Neck
- Liver
- Liver Transplant
- LMIC
- Lumbar Spinal Fusion
- Neonatal
- Obstetrics
- Oesophagectomy
- Orthopaedic
- Pancreatic
- Thoracic
- Urology
- Vascular

ERAS® Guidelines

All ERAS® Society Guidelines are available free at the ERAS® Society website

Cytoreductive surgery

Coming Soon

DEPARTMENT OF SURGERY RAMATHIBODI HOSPITAL

Pain management after open colorectal surgery

An update of the systematic review and procedure-specific postoperative pain management (PROSPECT) recommendations

Thomas Uten, Maximilien Chesnais, Marc van de Velde, Johan Raeder and Hélène Beloeil, on behalf of the PROSPECT Working group of the European Society of Regional Anaesthesia Pain therapy (ESRA)

Table 1 **Recommended pre, intra- and postoperative interventions**

Type of intervention	Recommendation
Intra-operative drugs	i.v. paracetamol and NSAID/COX-2 inhibitors are recommended for colonic surgery; paracetamol is recommended for rectal surgery.
	i.v. lidocaine when epidural analgesia is not feasible or contra-indicated
Regional techniques	Preoperative bilateral TAP block if TEA is not feasible or contra-indicated
	Low continuous TEA
Surgical techniques	Laparoscopic colorectal surgery over open colon surgery
	Diathermy over the scalpel.
	Horizontal/curved (transverse) incision over a vertical incision
Postoperative drugs	i.v. paracetamol and NSAID/COX-2 inhibitors are recommended for colonic surgery; paracetamol is recommended for rectal surgery.
	i.v. opioids as rescue
	i.v. lidocaine when epidural is not feasible or contra-indicated
	Continuous preperitoneal infusion of LA when epidural analgesia is not feasible or contraindicated.
	Low continuous TEA

i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug, TAP, transversus abdominis plane, TEA, thoracic epidural analgesia.

PROcedure-SPECific postoperative pain management guideline for laparoscopic colorectal surgery

A systematic review with recommendations for postoperative pain management

Philipp Lirk, Joy Badaoui, Marlene Stuempflen, Mona Hedayat, Stephan M. Freys and Girish P. Joshi, for the PROSPECT group of the European Society for Regional Anaesthesia and Pain Therapy (ESRA)*

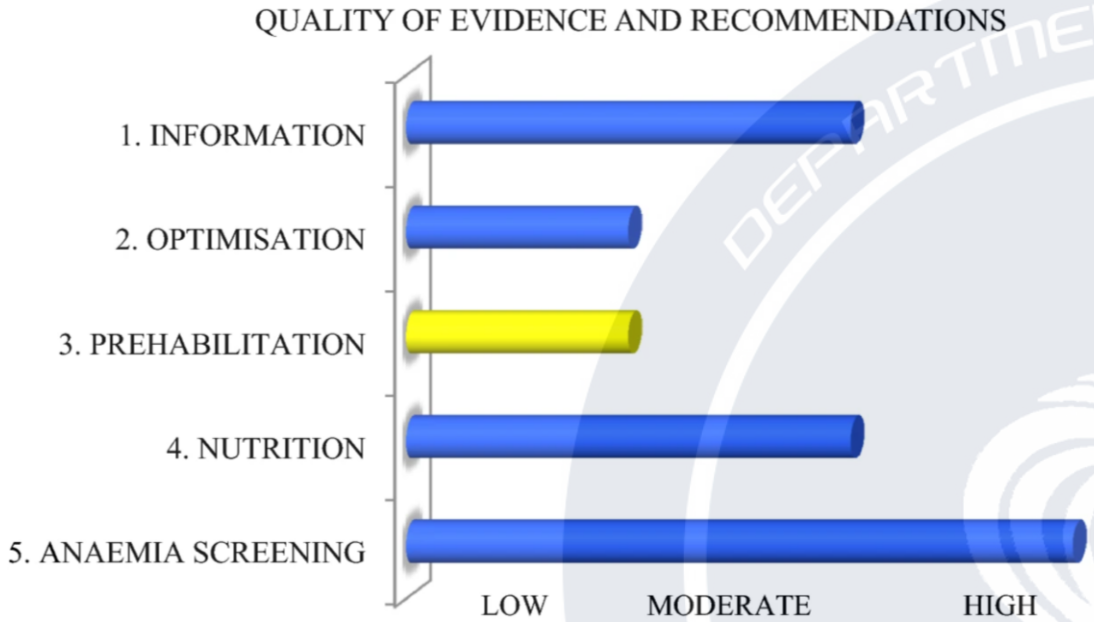
Table 1 **Overall recommendations for pain management following laparoscopic colorectal surgery**

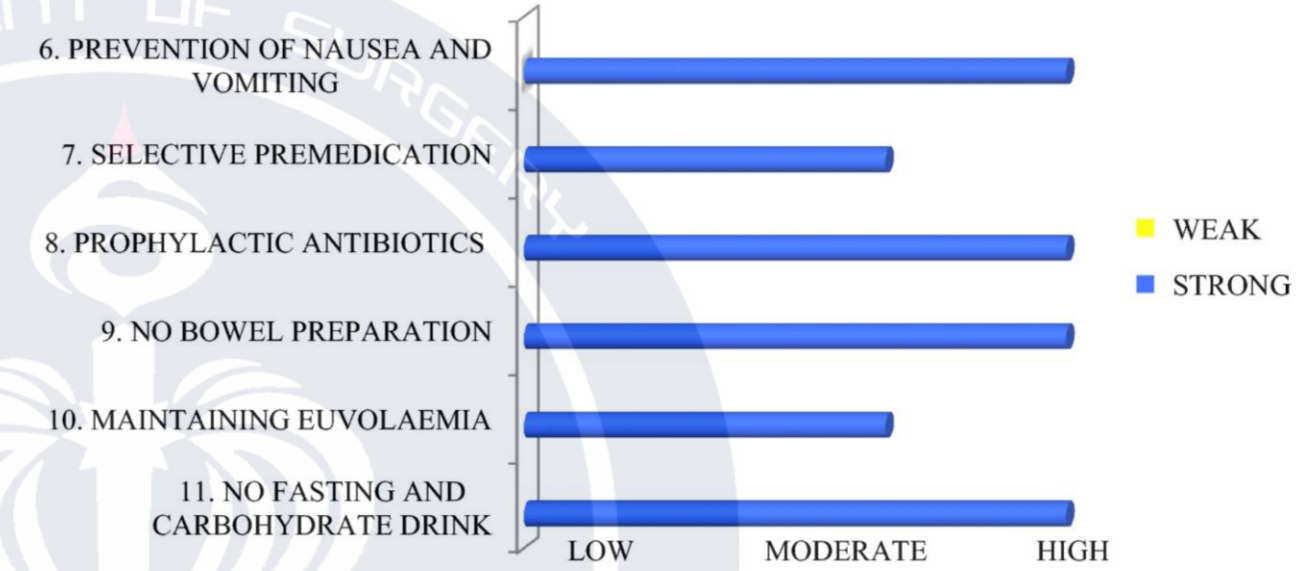
Paracetamol and nonsteroidal anti-inflammatory drugs, administered preoperatively or intra-operatively (if no contraindications)	Recommended
Surgical port site wound infiltration	Recommended
Rescue opioids	Recommended
Intravenous lidocaine	No consensus reached, may be used when basic analgesia cannot be provided
Spinal morphine	No consensus reached

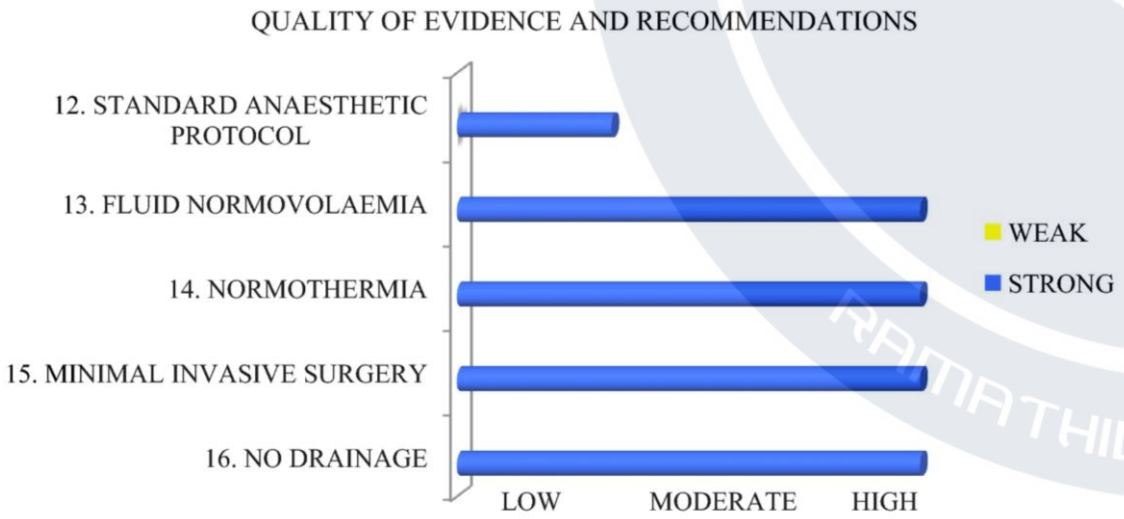
Table 2 **Interventions that are not recommended for pain management following laparoscopic colorectal surgery**

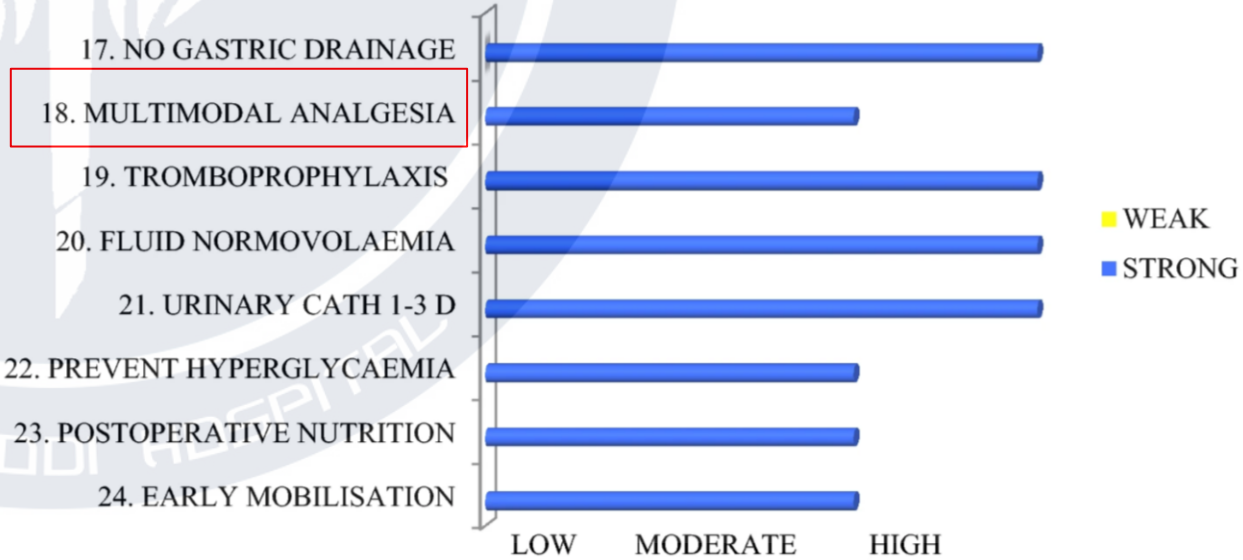
Interventions	Reasons for not recommending
Intraperitoneal local anaesthetics	Inconsistent evidence, may be used when basic analgesia or intravenous lidocaine cannot be provided
Deep neuromuscular blockade	Limited procedure-specific evidence
Epidural analgesia	Comprehensive risk–benefit assessment
Truncal blocks	Inconsistent procedure-specific evidence
Specific surgical techniques	Lack of procedure-specific evidence

From: Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018









Postoperative analgesia for colorectal surgery (ERAS®) Society Recommendations: 2018

- Postoperative analgesia resulting in adequate pain control is **essential in enhanced recovery pathways** in colorectal surgery.
- Although colon and rectal surgery (open and laparoscopic) differ considerably regarding technique, surgical trauma and early outcome.
- **Opioid avoiding or sparing techniques** in both types of surgery are associated with early mobilisation, fast return of bowel function, fewer complications and a reduction in LOS. Therefore, the key is to **avoid opioids and apply multimodal analgesia** in **combination with epidural analgesia (in open surgery)** when indicated.
- In fact, this multimodal strategy should ideally be included in the intraoperative period already and be a **continuum postoperatively** .

Complications of epidural analgesia

- LA
  - Hypotension
  - LAST (local anesthetic systemic toxicity)
  - Weakness
- Opioid
  - OIVI (opioid induced ventilatory insufficiency)
  - Nausea and vomit
  - Pruritus
  - Urinary retention

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Department	Division	Ward
Attending Staff	Resident	

ชื่อ.....
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DOCTOR' S ORDER SHEET FOR CONTINUOUS EPIDURAL ANALGESIA

Date / Hour	Orders for 1 day	Date / Hour	Continuous order (ขณะได้รับ Continuous epidural analgesia)	Date/Hour OFF

❑ Bolus Morphine dose……..mg. via epidural catheter at…… น.

▪ งด opioids และ sedative drugs ทุกชนิดและทุก route ถึง……

▪ กรุณาแจ้งวิสัญญีแพทย์ก่อนให้ยาละลายลิ่มเลือดและ/ หรือยาต้านการแข็งตัวของเลือดทุกชนิด

ชนิดของยาหยดเข้า Epidural space

❍ Premixed

❑ **0.1%** Bupivacaine total volume **300** ml

❑ **0.08 %** Bupivacaine total volume **250** ml

❍ ผสมเอง

_____% Bupivacaine total volume _____ml

(ผสม 0.5%Bupivacaine_____ mg (_____ml) in NSS _____ml)

Total volume	❍ 0.08% Bupivacaine			❍ 0.1% Bupivacaine		
	0.5% Marcaine		0.9%Nacl	0.5% Marcaine		0.9%Nacl
	mg	ml	ml	mg	ml	ml
❍ Volume 250 ml	200	40	210	250	50	200
❍ Volume 300 ml	240	48	252	300	60	240
❍ Volume 500 ml	400	80	420	500	100	400

ผสมกับ

❑ Fentanyl ความเข้มข้น…… mcg/ml

❑ Morphine ความเข้มข้น……mg/ml

Bupivacaine (Total volume)	❑ Fentanyl (50 mcg /ml)				❑ Morphine (10 mg/ml)			
	❑ 1 mcg /ml		❑ 2 mcg /ml		❑ 0.01 mg/ml		❑ 0.02 mg/ml	
	mcg	ml	mcg	ml	mg	ml	mg	ml
❍ Volume 250ml	250	5	500	10	2.5	0.25	5	0.5
❍ Volume 300ml	300	6	600	12	3	0.3	6	0.6
❍ Volume 500ml	500	10	1000	20	5	0.5	10	1

วิธีการบริหารยา

❍ Loading dose …….. ml

❍ Infusion rate …….. ml/hr

❍ Intermittent bolus……..ml per ……..hr

❍ PCEA dose ……..ml/dose

❍ Lockout interval ……. min

❍ Dose limit ……..ml per ……..hr

……

สายได้รับการตรวจสอบ และต่อกับขวดยา โดย

1).....CODE……

2).....CODE ……

Signature……..……CODE……

Monitoring

▪ Pain score : NRS* q 4 hr

▪ Sedation score (SS▲) q 4 hr

▪ **Modified Bromage scale▼** q 4 hr

▪ Bladder distension q 8 hr.

ถ้าไม่มีปัสสาวะใน 8 hr. และมี bladder full ให้ intermittent urinary catheterization

▪ Vital signs q 2 hr ถึง.....ต่อจากนั้น q 4 hr

▪ ถ้า SS▲ ≥ 3 และ RR ≤ .....ครั้ง/นาที กระตุ้นให้ผู้ป่วยหายใจ on O_2 mask with bag 8 L/min notify APS หรือแพทย์เวรวิสัญญีฯ และเตรียม naloxone (0.4 mg/amp) ที่ ward

Medication

❑ **Tramadol** Sig……. mg IV (slowly push) p.r.n. q …… hr for pain

❑ **Ondansetron** Sig……mg IV p.r.n. q……. hr for nausea/vomiting

❑ **Chlorpheniramine** Sig……mg IV p.r.n. q 6 hr for itching

……

……

……

……

……

……

……

……

Notify หน่วยระงับปวดเฉียบพลัน (Acute Pain Services :APS) ในเวลาราชการ โทร 48914 หรือนอกเวลาราชการ โทร 1593 / 1503 **(แพทย์เวรวิสัญญีวิทยา)** ถ้าผู้ป่วยปวดระดับมาก (NRS ≥7), มีขาอ่อนแรง (Modified Bromage scale▼ > 2), SS▲ ≥3 หรือ RR ≤ ..... ครั้ง/นาที หรือมีข้อสงสัยที่เกี่ยวข้อง

Signature ……. CODE……

NRS* (Numerical Rating Scale): 0 -10 SS▲ (Sedation Score) : S =นอนหลับปกติ 1 = ตื่นรู้สึกตัวดี 2 = ง่วงหลับบ้าง ปลุกตื่นง่าย 3 = ง่วงหลับเป็นส่วนใหญ่ ปลุกตื่นยาก 4 = ง่วงหลับมาก ปลุกไม่ตื่น

Modified Bromage scale▼ : 0 = ขยับได้ปกติ, 1 = ขยับในแนวตั้งได้แต่อ่อนแรงกว่าผู้ตรวจ, 2 = ขยับในแนวราบได้ แต่ขยับในแนวตั้งไม่ได้, 3 = ขยับไม่ได้เลย *(Version1, March 2024)*

RAMATHIBODI HOSPITAL

Department	Division	Ward
Attending Staff	Resident	

ชื่อ.....
HN .....
อายุ.....แผ่นที่.....

DOCTOR' S ORDER SHEET FOR INTERMITTENT SPINAL/EPIDURAL MORPHINE ANALGESIA

Date Hour	Orders for 1 day	Date / Hour	Continuous order	Date/Hour OFF

Post-operative order for intermittent

Spinal/Epidural Morphine analgesia

ประเภทของ Neuraxial opioid

❑ Spinal Morphine dose.....….....….mg at……

❑ Epidural Morphine dose…….....mg at……

▪ งด opioids และ sedative drugs ทุกชนิดและทุก route ถึง……

▪ Absolute bed rest 6 hrs ถึงเวลา……

Monitoring 24 hr.

▪ Pain score;NRS q 4 hr

▪ Sedation score (SS▲) q 4 hr

▪ Motor power▲ q 4 hr

▪ Bladder distension q 4 hr ถ้าไม่มีปัสสาวะใน 4 hr และมี bladder full ให้ intermittent urinary catheterization

▪ Vital signs : Respiratory rate (RR) q 4 hr. ถ้าRR ≤ 10 ครั้ง/นาที กระตุ้นให้ผู้ป่วยหายใจ on O_2 mask with bag 8 L/min notify APS หรือแพทย์เวรวิสัญญีฯ และเตรียม naloxone (0.4 mg/amp) ที่ ward

Medication

❑ **Tramadol** Sig……..mg IV(slowly push) p.r.n. q …. hr for pain

❑ **Ondansetron** Sig……..mg IV p.r.n. q ……. hr for nausea/vomiting

❑ **Chlorpheniramine** Sig…10…mg IV p.r.n. q 6 hr for itching

……

……

……

……

Notify หน่วยระงับปวดเฉียบพลัน (Acute Pain Services :APS)

ในเวลาราชการ โทร 48914 หรือนอกเวลาราชการ โทร 1593 / 1503

ถ้า SS▲ ≥3 หรือ RR ≤ 10 ครั้ง/นาที หรือมีข้อสงสัยที่เกี่ยวข้อง

Signature ……..……CODE……

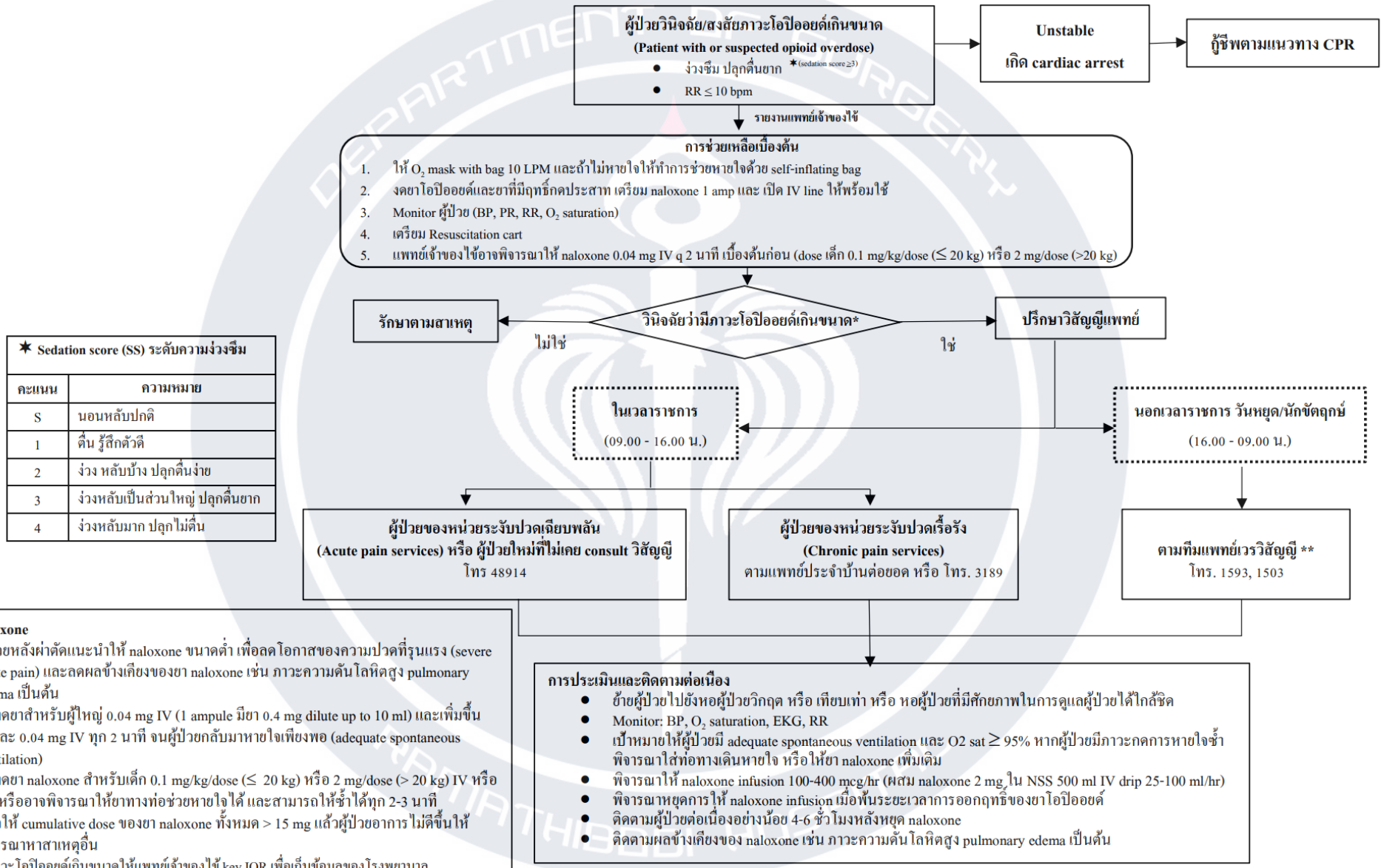
NRS* (Numerical Rating Scale): 0 -10

SS▲ (Sedation Score) : S =นอนหลับปกติ 1 = ตื่นรู้สึกตัวดี 2 = ง่วงหลับบ้าง ปลุกตื่นง่าย 3 = ง่วงหลับเป็นส่วนใหญ่ ปลุกตื่นยาก 4 = ง่วงหลับมาก ปลุกไม่ตื่น

Motor power▲ :
grade 0 = ไม่มีการหดตัวของกล้ามเนื้อ
grade I = มีการหดตัวของกล้ามเนื้อแต่ไม่มีการขยับในแนวราบ
grade II = ขยับในแนวราบได้ ขยับในแนวตั้งไม่ได้
grade III = ขยับในแนวตั้งได้ แต่อ่อนแรงกว่าผู้ตรวจ
grade IV = อ่อนแรงกว่าผู้ตรวจเล็กน้อย
grade V = ปกติ

(Version1, March 2024)

แนวทางปฏิบัติในการรักษาและส่งปรึกษาวิสัญญีแพทย์ในผู้ป่วยที่วินิจฉัย/ สงสัยภาวะโอปิออยด์เกินขนาด



★ Sedation score (SS) ระดับความง่วงซึม

คะแนน	ความหมาย
S	นอนหลับปกติ
1	ตื่น รู้สึกตัวดี
2	ง่วง หลับบ้าง ปลุกตื่นง่าย
3	ง่วงหลับเป็นส่วนใหญ่ ปลุกตื่นยาก
4	ง่วงหลับมาก ปลุกไม่ตื่น

Dose Naloxone

- ผู้ป่วยหลังผ่าตัดแนะนำให้ naloxone ขนาดต่ำ เพื่อลดโอกาสของความปวดที่รุนแรง (severe acute pain) และลดผลข้างเคียงของยา naloxone เช่น ภาวะความดันโลหิตสูง pulmonary edema เป็นต้น
- ขนาดยาสำหรับผู้ใหญ่ 0.04 mg IV (1 ampule มียา 0.4 mg dilute up to 10 ml) และเพิ่มขึ้นครั้งละ 0.04 mg IV ทุก 2 นาที จนผู้ป่วยกลับมาหายใจเพียงพอ (adequate spontaneous ventilation)
- ขนาดยา naloxone สำหรับเด็ก 0.1 mg/kg/dose (≤ 20 kg) หรือ 2 mg/dose (> 20 kg) IV หรือ IM หรืออาจพิจารณาให้ยาทางท่อช่วยหายใจได้ และสามารถให้ซ้ำได้ทุก 2-3 นาที
- หากให้ cumulative dose ของยา naloxone ทั้งหมด > 15 mg แล้วผู้ป่วยอาการไม่ดีขึ้นให้พิจารณาหาสาเหตุอื่น

* วินิจฉัยภาวะโอปิออยด์เกินขนาดให้แพทย์เจ้าของไข้ key IOR เพื่อเก็บข้อมูลของโรงพยาบาล

** แพทย์เวรวิสัญญีพิจารณาปรึกษาแพทย์ประจำบ้านต่อยอด (Fellow Pain) เวรนอกเวลา กรณีเป็นผู้ป่วยของ chronic pain service ถ้าเป็นผู้ป่วยใหม่ หรือ ผู้ป่วยของหน่วยระงับปวดเฉียบพลันพิจารณาปรึกษา

การประเมินและติดตามต่อเนื่อง

- ย้ายผู้ป่วยไปยังหอผู้ป่วยวิกฤต หรือ เทียบเท่า หรือ หอผู้ป่วยที่มีศักยภาพในการดูแลผู้ป่วยได้ใกล้ชิด
- Monitor: BP, O2 saturation, EKG, RR
- เป้าหมายให้ผู้ป่วยมี adequate spontaneous ventilation และ O2 sat ≥ 95% หากผู้ป่วยมีภาวะกดการหายใจซ้ำ พิจารณาใส่ท่อทางเดินหายใจ หรือให้ยา naloxone เพิ่มเติม
- พิจารณาให้ naloxone infusion 100-400 mcg/hr (ผสม naloxone 2 mg ใน NSS 500 ml IV drip 25-100 ml/hr)
- พิจารณาหยุดการให้ naloxone infusion เมื่อพ้นระยะเวลาการออกฤทธิ์ของยาโอปิออยด์
- ติดตามผู้ป่วยต่อเนื่องอย่างน้อย 4-6 ชั่วโมงหลังหยุด naloxone
- ติดตามผลข้างเคียงของ naloxone เช่น ภาวะความดันโลหิตสูง pulmonary edema เป็นต้น

Interfascial plane block

- Mechanism
  - Local dispersion
    - Bulk flow (pressure gradient)
    - Diffusion (concentration gradient)
  - Systemic effect of LA
- Cause of block inconsistency
  - Fascial structure (thickness of fascial plane, line of fusion, fascia interconnectivity)
  - Fascial function (fascial gliding, viscosity, HA, gycoaminoglycan, fasciacyte, temperature, pH)
  - Interfascial journey of nerves (nerve variation)
  - Other possible factors (site of injection, volume, needle size, direction of injection, tissue laxity, patient position, speed of injection, injection pressure)

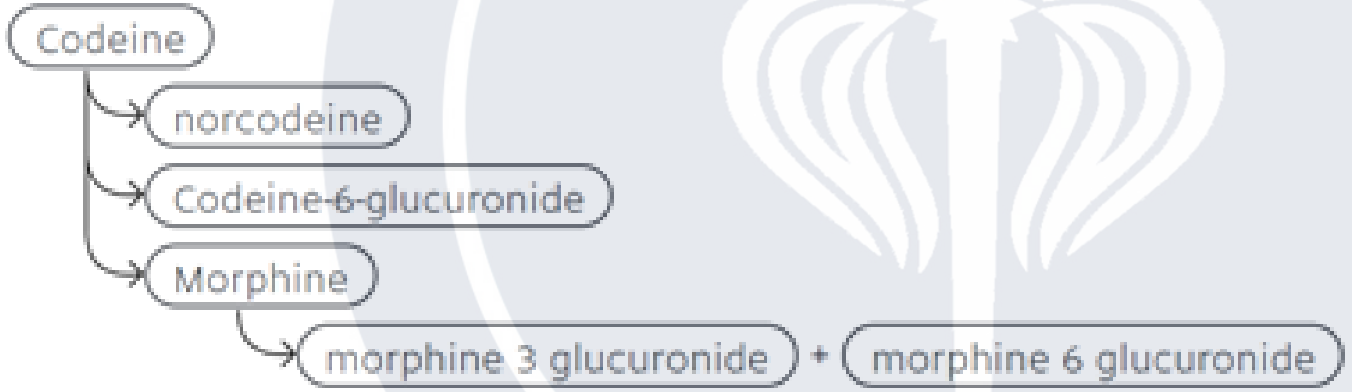
Multimodal Analgesia Drugs

Weak opioids

- Codeine
- Tramadol

Codeine

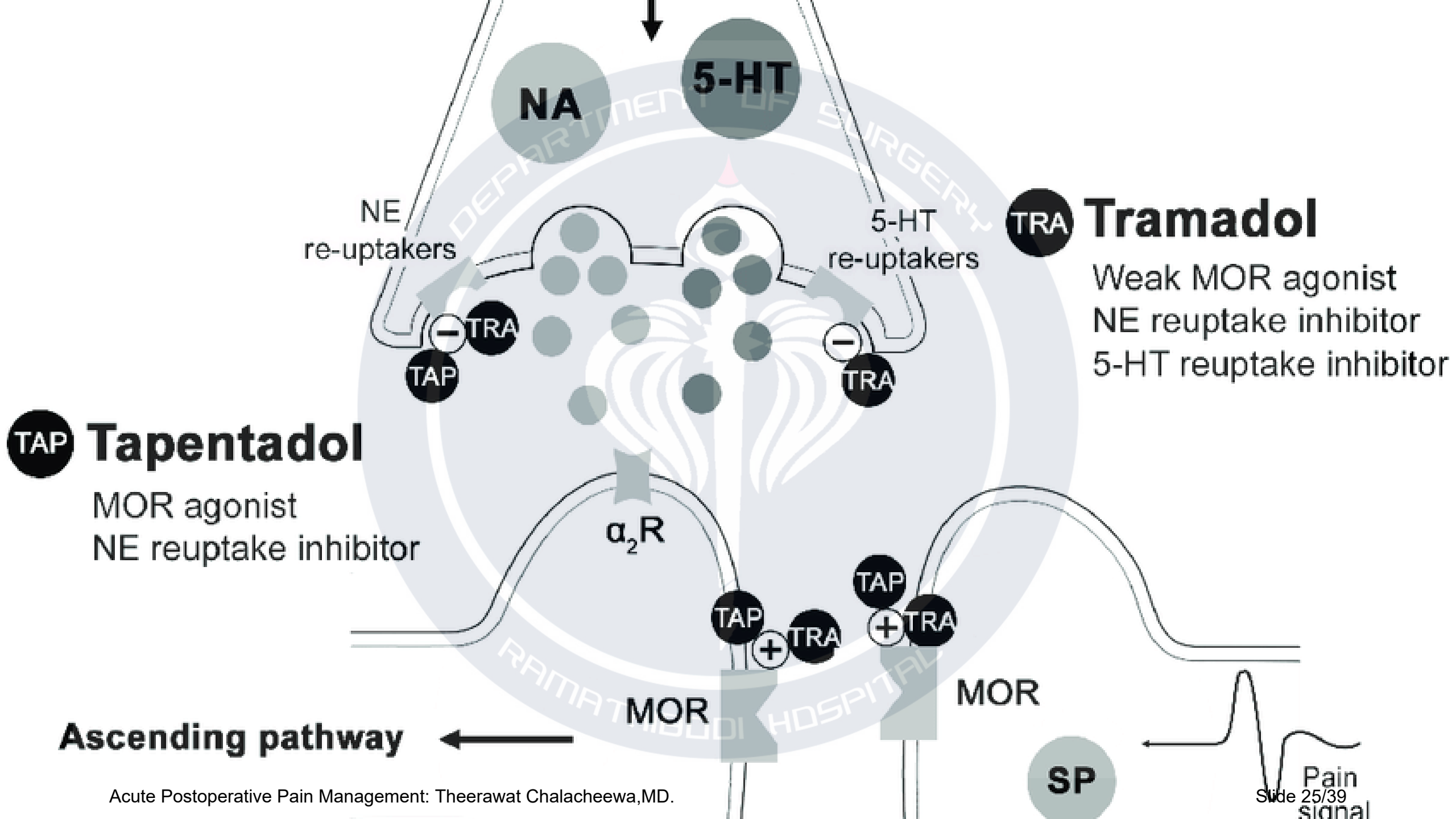
- Weak narcotic pain reliever and cough suppressant similar to morphine and hydrocodone
- Metabolism



- Maximum dose ; 120 mg/24 h

Tramadol

- Tramadol has an oral absorption of 100%, with a mean bioavailability of 70% owing to a 20% to 30% first-pass metabolism after a single oral dose.
- Binds weakly to κ- and δ-opioid receptors and to the μ-opioid receptor
- The major active metabolite is O-desmethyl-tramadol (M1), which displays a μ-opioid receptor affinity 300 times greater than that of the parent drug
- SNRI (serotonin/norepinephrine reuptake-inhibitor)
- Maximum dose 400 mg/24 h
- The maximum dose of tramadol prescribed to advanced CKD patients (GFR<30) has been suggested to not exceed 50 mg orally twice a day


NA
5-HT
NE
re-uptakers
5-HT
re-uptakers
TRA
TAP
TRA
TRA
Tramadol
Weak MOR agonist
NE reuptake inhibitor
5-HT reuptake inhibitor
TAP
Tapentadol
MOR agonist
NE reuptake inhibitor
α2R
TAP
TRA
TAP
TRA
MOR
MOR
Ascending pathway
SP
Pain
signal

Acetaminophen (paracetamol)

- Indication
  - Treatment of mild-to-moderate pain
- Mechanism
  - Preferential inhibitor of COX-2 isoenzyme
  - Stimulate effect of descending serotoninergic pathways
  - Modulation of opioid system
  - Increase activity of endocannabinoid system
  - Inhibit nitric oxide production

Paracetamol toxicity: Warnings

- Keep total daily dose not more than 4 g/day (which is the maximum daily dose) / be aware of using combination product
- Lower dose in patient with
  - Chronic alcoholism/ regularly alcohol intake >3 drink/day
  - Concomitant use of enzyme inducer
  - Malnutrition, old age, liver disease
- Potentiation of warfarin effect was found (≥2 g/day of paracetamol for at least 3 consecutive days → INR should be tested 3 to 5 days after the first paracetamol dose)

Acta Poloniae Pharmaceutica - Drug research 2014;71(1):11-23
J Clin Pharm Ther 2012;37:681-5.
Blood 2011;118:6269-73.

Non-Steroidal Anti-inflammatory Drugs

Mechanism

Prostaglandin synthesis

- These prostanoids are important **mediators of pain and hyperalgesia** in response to inflammation and tissue injury but also critically to **many homeostatic body function**
- **COX** catalyzed peroxidation of AA

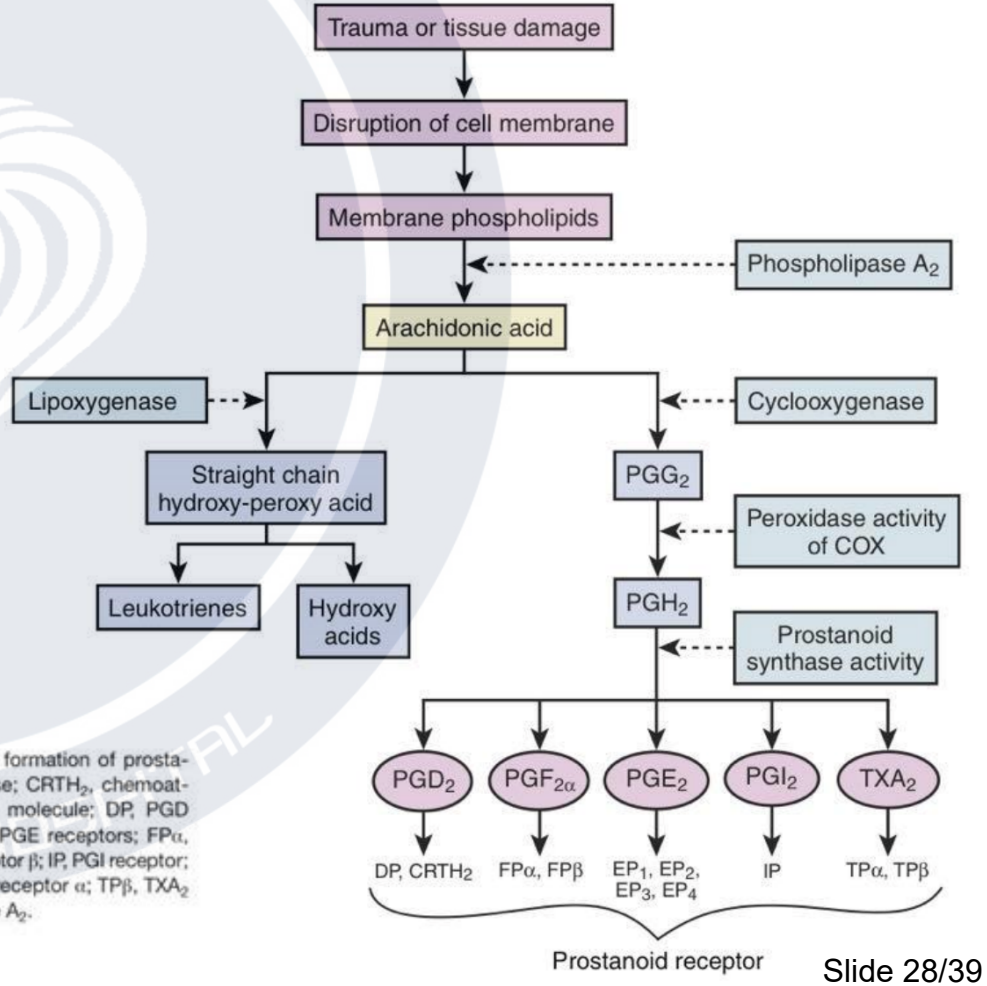
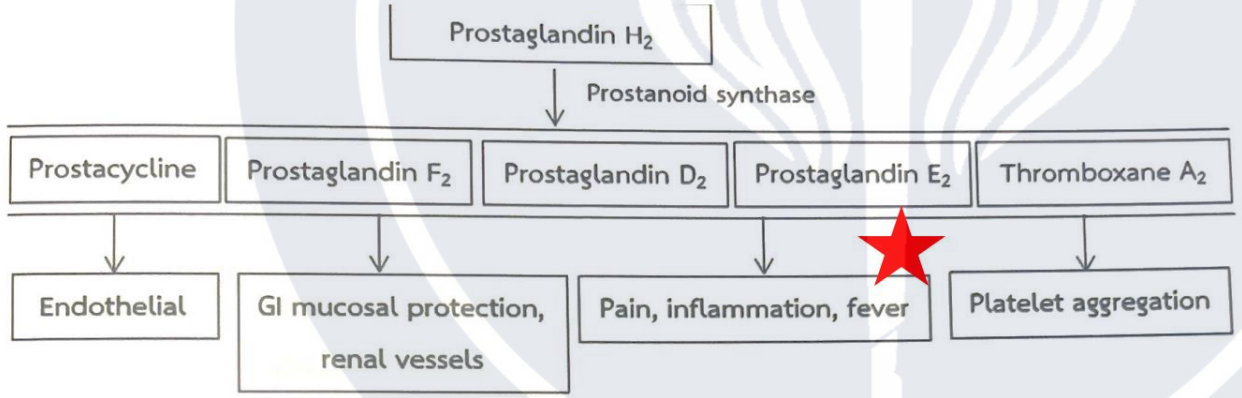


Figure 40.2 Pathway for the formation of prostaglandins. COX, cyclooxygenase; $CRTH_2$, chemoattractant receptor-homologous molecule; DP, PGD receptor; EP_1, EP_2, EP_3, EP_4, PGE receptors; FPα, PGF receptor α; FPβ, PGF receptor β; IP, PGI receptor; PG, prostaglandin; TPα, TXA_2 receptor α; TPβ, TXA_2 receptor β; TXA_2, thromboxane A_2.

Non-Steroidal Anti-inflammatory Drugs

Mechanism

Prostaglandin synthesis

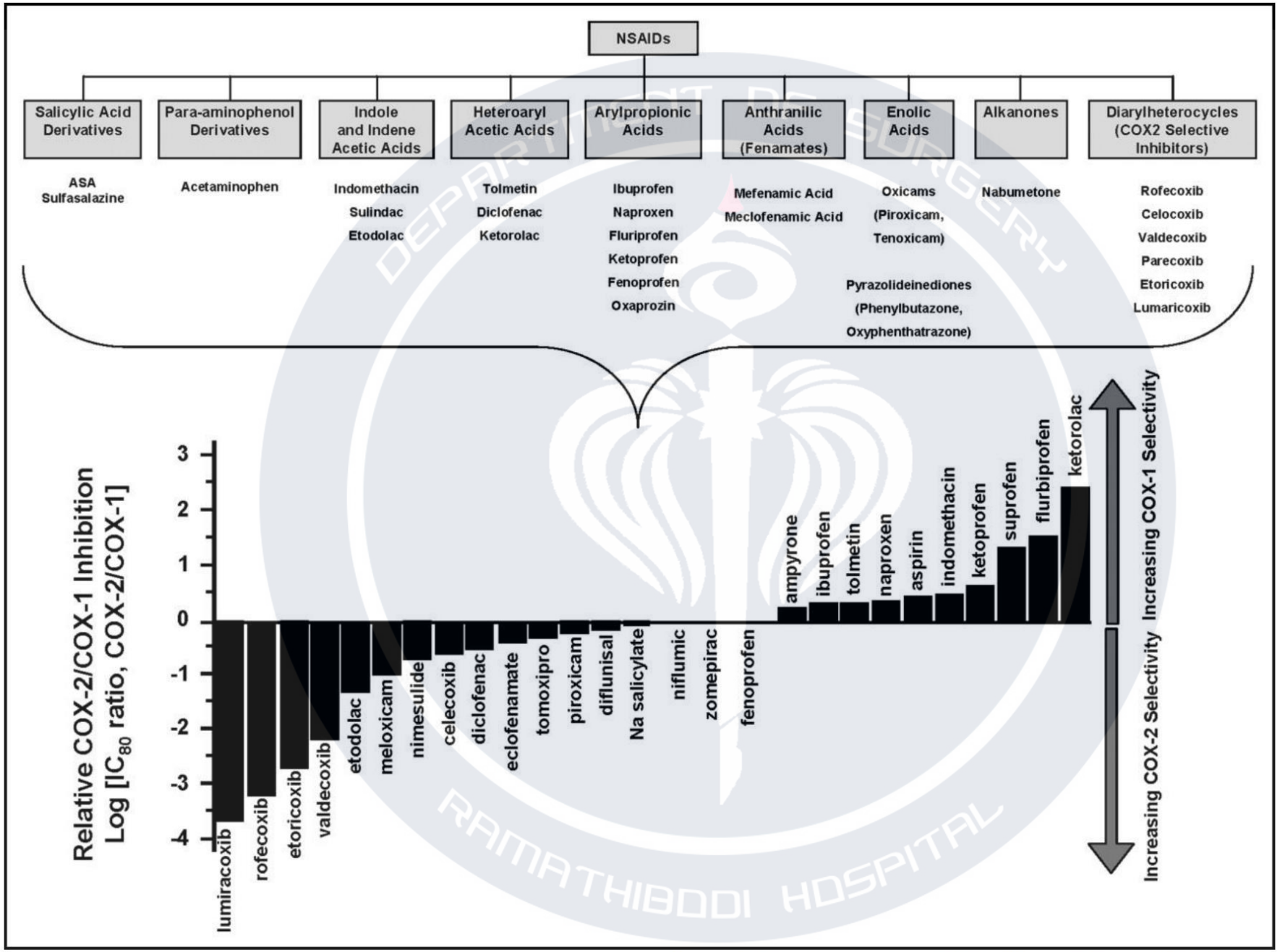


- **PGE2** → the most important prostaglandin in both peripheral and central pain sensitization

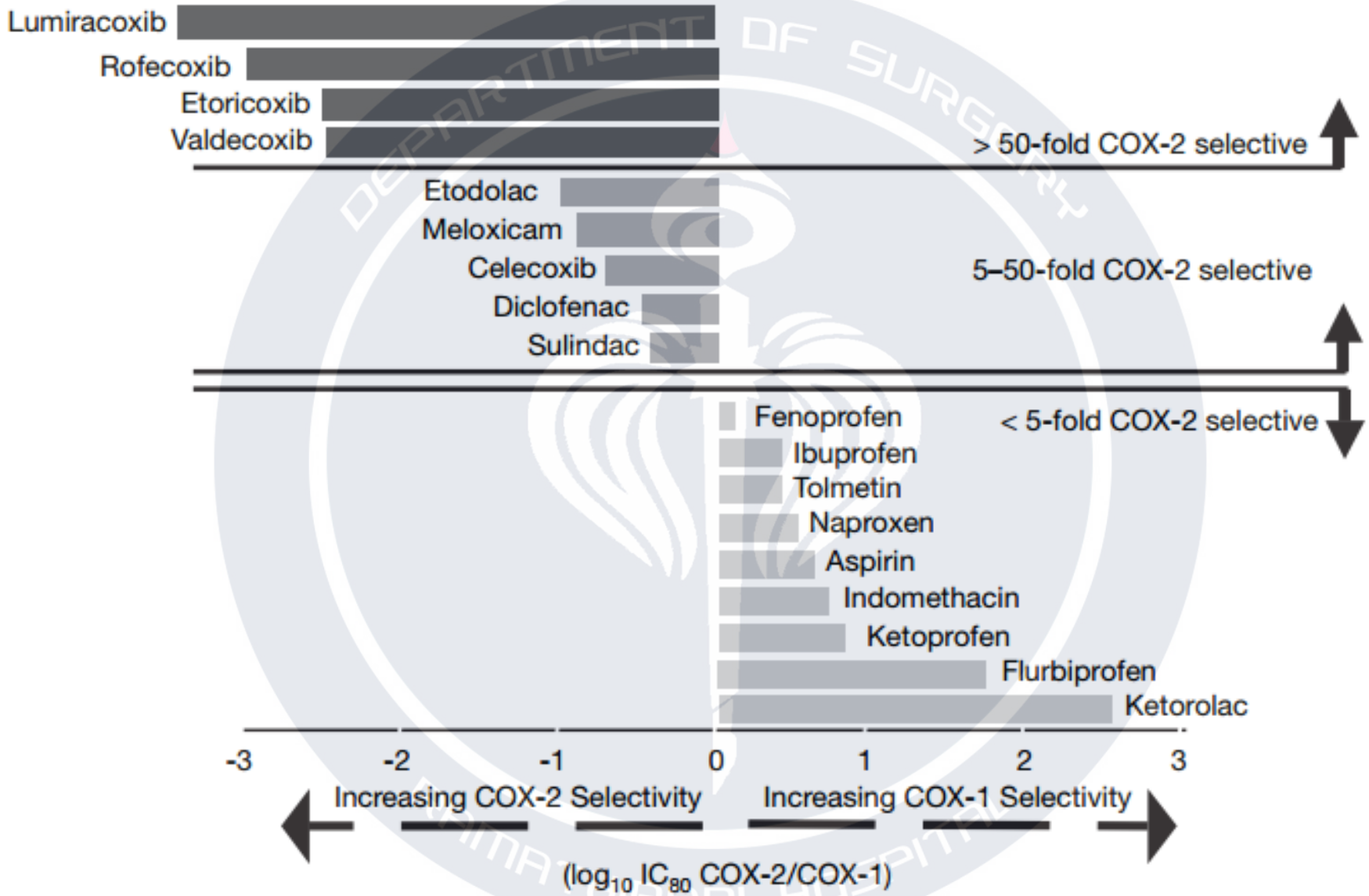
Tissue/organ	Mediators	Function(s)
Female reproductive organs	PGE_2, $PGF_{2\alpha}$	Uterine contraction, oxytocic action
Male reproductive organs	PGE_2, $PGF_{2\alpha}$	Fertility
Cardiovascular system	TXA_2, PGI_2 TXA_2 PGE_2, PGI_2 TXA_2, $PGF_{2\alpha}$ PGE_2, PGI_2	Thrombosis, platelet aggregation Vascular permeability Arterial vasodilation Venous vasoconstriction Patency of the fetal ductus arteriosus
Respiratory system	PGE_2 $PGF_{2\alpha}$, TXA_2	Bronchodilation Bronchoconstriction
Renal system	PGE_2, PGI_2 PGE_2, PGI_2 PGE_2	Regulation renal blood flow and glomerular filtration rate Renin release Inhibition hydro-osmotic effect of ADH
Gastrointestinal system	PGE_2, PGI_2	Cytoprotection
Immune system	PGE_2, PGI_2	Inhibition T and B lymphocyte activation and proliferation
Central nervous system	PGE_2 PGD_2 PGE_2, PGI_2	Fever Sleep Pain

ang D. PROSTAGLANDINS AND CANCER. Gut. 2006 Jan 1;55(1):115-22.

ohinoyi DA, Morebise O,Fakoya AOJ. Mechanism of inflammatory pain and olementation of natural products as rescue route. J Pharm Biomed Sci



Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis. Proc Natl Acad Sci USA. 1999 Jun 22;96(13):7563-8.

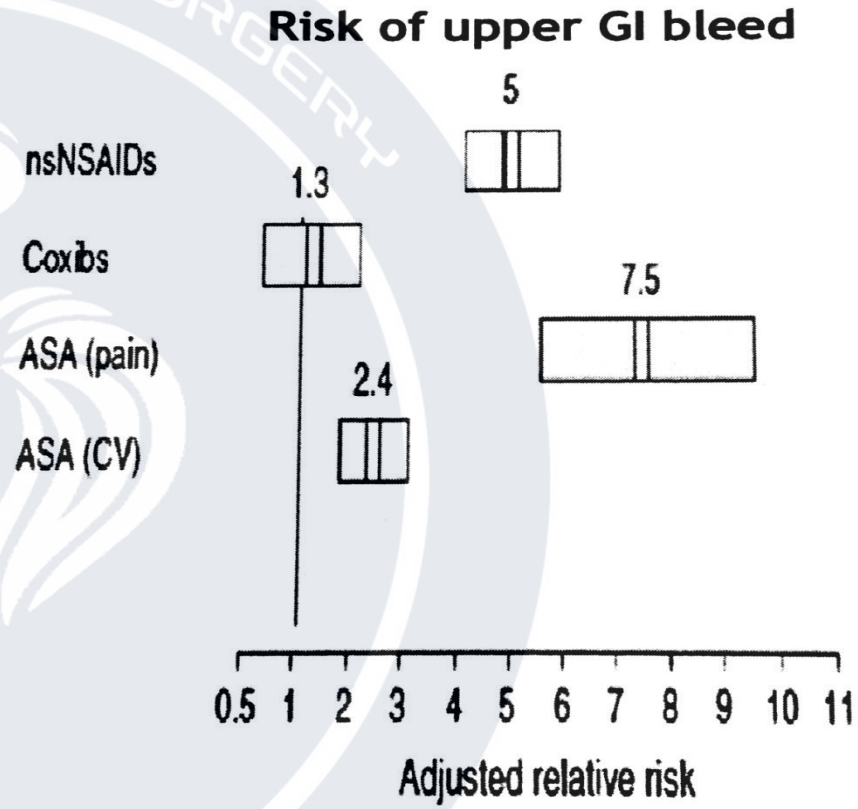


Adapted from: Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. FASEB J 2004;18(7):790-804.

Adverse Effects of tNSAIDs/Coxibs

All NSAIDs

- Gastroenteropathy - gastritis, bleeding, ulceration, perforation (tNSAIDs > COXIBs)
  - Cardiovascular
    - Thrombotic events
    - CHF
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Allergic phenomenon



Cox-1-mediated NSAIDs (tNSAIDs)

- Decreased platelet aggregation (tNSAIDs are contraindicated in chemotherapy-induced thrombocytopenia)

Coxib = cyclo-oxygenase-2 selective inhibitor; NSAID = nonsteroidal anti-inflammatory drug; nsNSAID = non-specific NSAID
Clemett D, Goa KL. Drugs 2000; 59(4):957-80; Grosser T et al. In: Brunton L et al (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th edition. New York, NY: McGraw-Hill; 2010.

For patients at risk for GI Ulceration and/or Bleeding, consider the following:

- All NSAIDs are associated with some level of increased risk for GI complications so it is best to use the lowest effective dose for the shortest duration of time
- **Lowest risk** for GI complications: **Ibuprofen and celecoxib***
- **Relatively low risk** for GI complications: **Meloxicam, etodolac* and nabumetone***
- **High** (i.e. twice the risk associated with ibuprofen) for GI complications: **Naproxen, indomethacin and diclofenac***
- **Highest risk** for GI complications: **Ketorolac and piroxicam***

GI Risk Factors[1]	GI Risk Classification[1]
• Age > 65 years • High dose NSAID therapy • Previous history of uncomplicated ulcer Concurrent aspirin, anticoagulant, or corticosteroid use	• Low: No risk factors • Moderate: 1-2 risk factors • High: > 2 risk factors OR Previous complicated ulcer

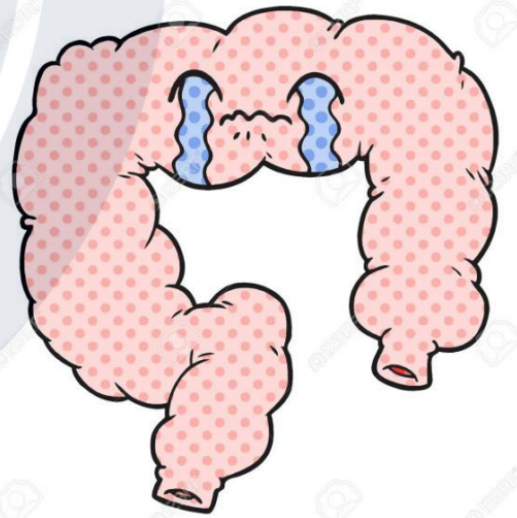
PRESCRIBING NSAIDS IN PATIENTS WITH CERTAIN RISK FACTORS

Patient Risk Factors	Low GI Risk	Moderate GI Risk	High GI Risk
Low CV Risk	Ibuprofen **OR** other low-GI risk NSAID	1. Low-GI risk NSAID + generic PPI 2. Low-GI risk NSAID +generic double-dose H_2-blocker (2nd line) 3. Celecoxib* alone (most expensive choice)	1. Avoid NSAIDs if possible 2. Celecoxib*+ PPI
High CV Risk‡	Naproxen	1. Naproxen + PPI 2. Naproxen + double-dose H_2 blocker (2nd line)	Avoid NSAIDs

‡High CV risk defined as patients requiring low-dose aspirin for prevention of serious CV events

Anastomosis leakage

- In rodent models shown reduced collagen formation after given diclofenac (klein 2012)
- the two most recent meta-analysis of primarily cohort show an increased anastomosis leak rate with nsNSAIDs. *(Modasi 2019 level III)* (OR 2.02; 95%CI 1.62 to 2.50 and OR 1.79; 95%CI 1.47 to 2.18 respectively)
- There is no increased leakage rate with perioperative coxibs *(Modasi 2019 level III)*



Acute Pain Management: Scientific Evidence 5th ed. Australian and NZ College of Anaesthetists and Faculty of Pain Medicine 2020.

Allergy

- NSAID especially nsNSAID are most common cause of drug induced hypersensitivity
- N-ERD has prevalence of 1.8% and affects 10%-20% of adult with asthma and 5% of children with asthma (Kowalski 2)
- Bronchospasm usually occurs within 1-2 hours of exposure and precipitation related to COX-1 activity
- While both COX-2 selective and COX-2 preferential inhibitors (nimesulide and meloxicam) usually well tolerated
- Coxibs administered at analgesic dose→ do not produce bronchospasm in patients with NSAID-exacerbate respiratory disease (level I)

How do you choose right NSIADs

- Choosing the right NSAID for an individual patient requires that the relative risks for each type of side effect be considered

Nefopam

- Indication
  - Treatment of moderate-severe pain
- An orphenadrine derivative
- is not an opiate and a non-steroidal anti-inflammatory drug.
- Na and Ca channel blocker
- It inhibits the reuptake of serotonin, dopamine, and noradrenaline
- It does not cause respiratory depression.
- Various adverse reactions have been reported, including nausea, vomiting, epigastric pain, dizziness, drowsiness and mental confusion, hypotension, tachycardia, skin rashes, xerostomia, and urinary retention

Nefopam (Acupan)

NEFOPAM

RCCP Ramathibodi Conference of Clinical Pharmacy

ข้อบ่งใช้: ควบคุมการปวดภายหลังการผ่าตัด (post-operative pain)

Nefopam มี 2 รูปแบบ ได้แก่

1. รูปแบบฉีด 20 mg/2 ml
2. รูปแบบรับประทาน ขนาด 30 mg

ในประเทศไทยมีการขึ้นทะเบียนยาเฉพาะรูปแบบยาฉีดเท่านั้น

ขนาดยาและการบริหารยา nefopam

IV bolus infusion: 20 mg every 4 to 6 hours as needed (maximum: 120 mg/day)

Continuous infusion: 80 mg IV drip in 24 hr

Recommend nefopam 20 mg infuse 45-60 นาที

เพื่อลดผลข้างเคียง: หัวใจเต้นเร็ว คลื่นไส้อาเจียน มึนศีรษะ เหงื่อออก

** NET: norepinephrine transporter, **SERT: serotonin transporter*

กลไกการออกฤทธิ์ของ nefopam

1. เพิ่มการทำงานของ descending inhibitory pain pathway โดยยับยั้ง NET*, SERT**
2. ยับยั้ง voltage sensitive sodium channels (VSSCs) และ voltage sensitive calcium channels (VSCCs)

ข้อห้ามใช้ของยา nefopam

- ผู้ป่วยเด็กที่**อายุน้อยกว่า 15 ปี**
- สตรี**ตั้งครรภ์**และสตรี**ให้นมบุตร**
- ผู้ป่วยที่มีประวัติหรืออาการ**โรคลมชัก**
- ผู้ป่วยที่มีความเสี่ยงในการเกิด **urinary retention**
- ผู้ป่วยที่มีความเสี่ยงในการเกิด **acute angle glaucoma**

ข้อควรระวังเกี่ยวกับ nefopam

- อาจทำให้เกิด serotonin syndrome เมื่อให้ร่วมกับ SSRIs, SNRIs, tramadol, pethidine
- ระวังการใช้ nefopam ในผู้ที่มี cardiovascular disease
- ปรับขนาดยาในผู้ป่วยที่มีภาวะ hepatic failure และ renal failure

Thank you