



PARACETAMOL IV REDUCES OPIOID,
ANTIEMETIC CONSUMPTION & PONV

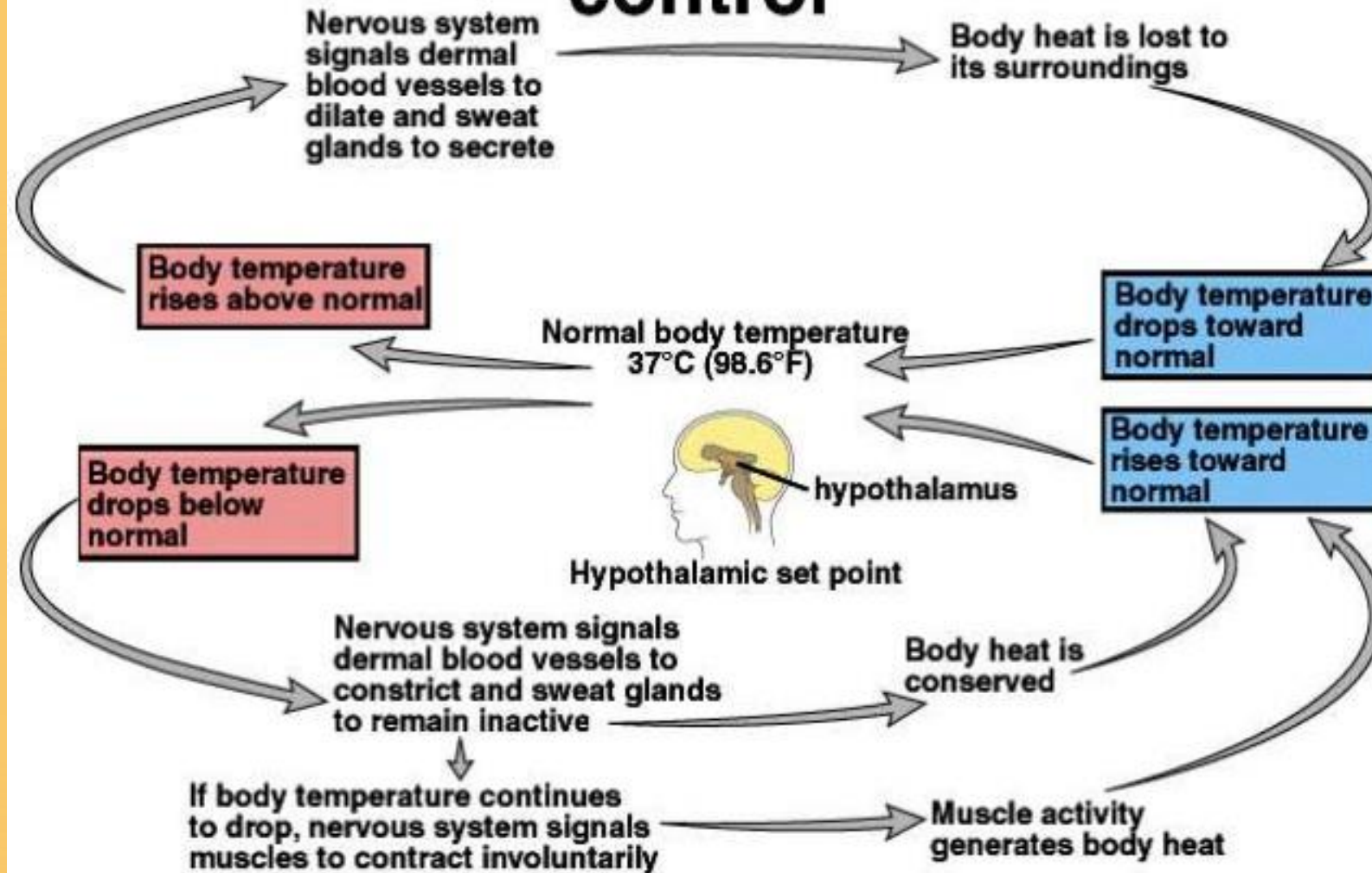
Introduction

- ▶ Thermoregulation is an essential homeostatic mechanism.
- ▶ Thermoregulation consists of afferent signalling ,central processing within the hypothalamus and efferent response.
- ▶ This circadian rhythm is altered in critically ill patients with both temporal shifts and a larger magnitude of variation, increases with disease severity.

Normal mean temperature

- ▶ The metabolic rate of humans produces consistently more heat than is necessary to maintain core body temperature of 98.6 °F.
- ▶ Oral: 98.2 +/- 0.7 °F
- ▶ Low at 6 am
- ▶ High at 4 to 6 pm
- ▶ AM temperature > 98.8°F
- ▶ PM temperature > 99.9 °F

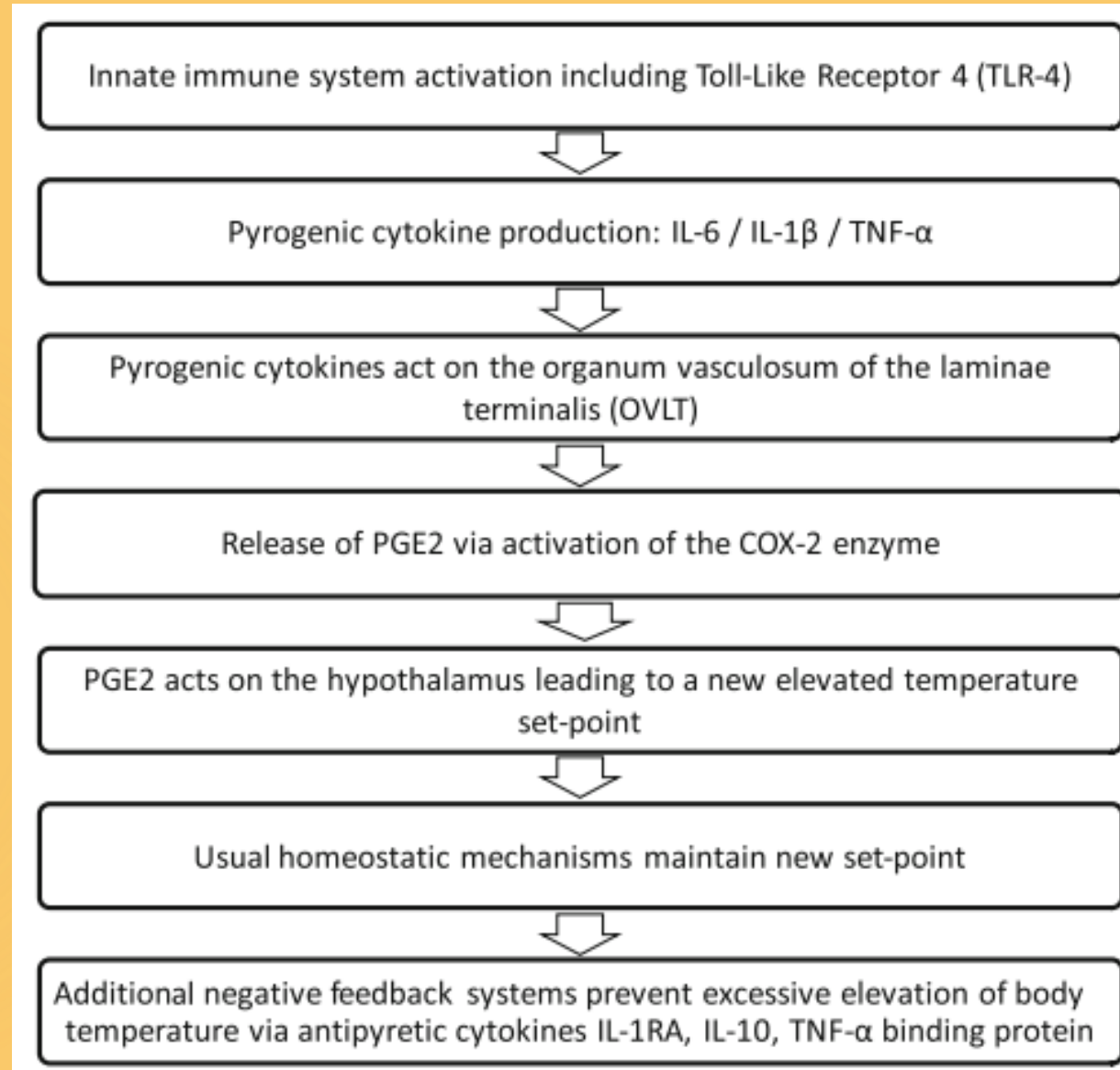
Homeostasis and temperature control



Pyrexia

- ▶ Pyrexia secondary to the systemic inflammatory response to be distinguished from hyperthermia seen in heatstroke and malignant syndromes or from ineffective heat loss.
- ▶ Temperature levels encountered during hyperthermia are usually higher than during pyrexia because thermoregulation is abolished.
- ▶ Indication of rapid temperature control is, therefore, indisputable to avoid irreversible tissue damage.

Pathogenesis of fever



Impact of pyrexia treatment on outcome

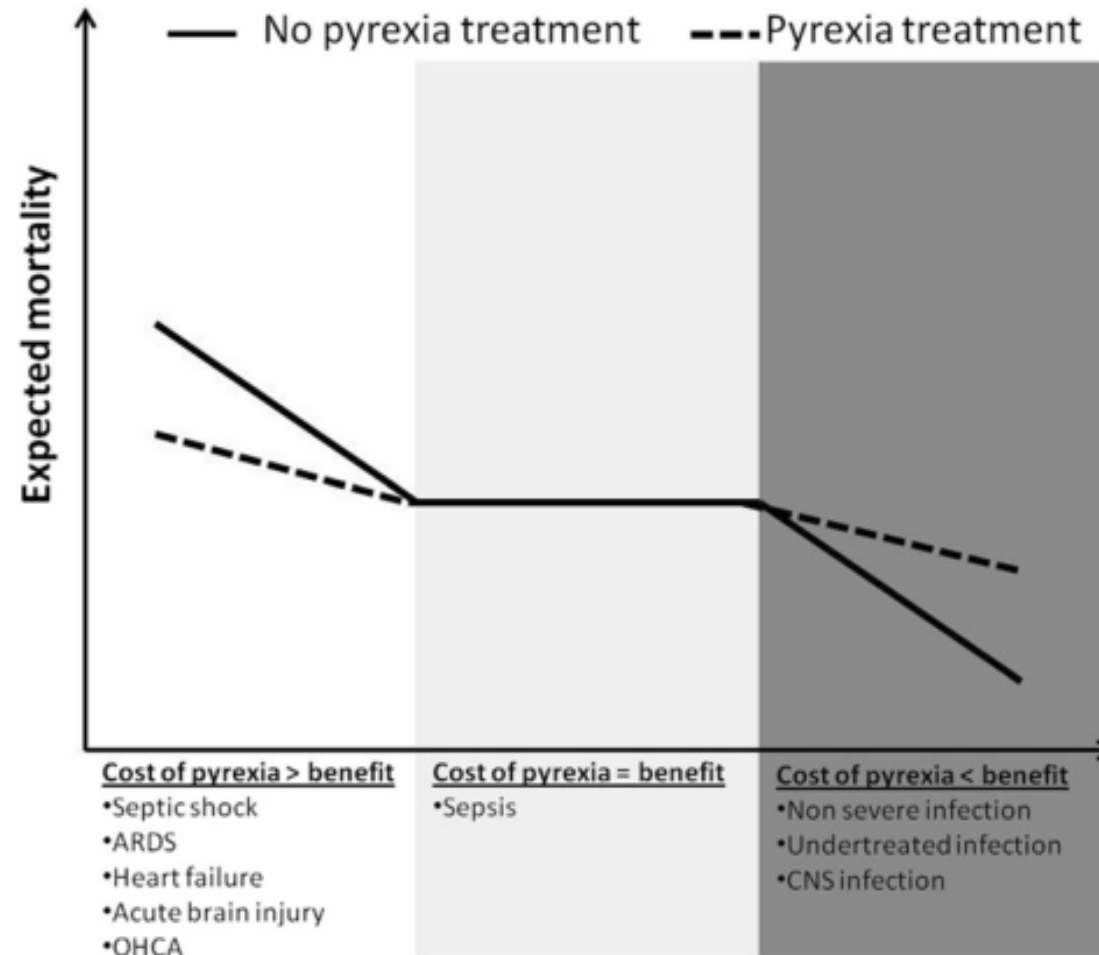


Fig. Suggested impact of pyrexia treatment on outcome according to clinical context. ARDS acute respiratory distress syndrome, CNS central nervous system, OHCA Out-of-hospital cardiac arrest

Need to treat fever

- ▶ The vast majority of fevers are associated with self-limited infections, mostly of viral origin, where the cause is easily identified.
- ▶ Fever may not be present during infection in newborns, older adults, patients with chronic renal failure, and in patients taking corticosteroids.
- ▶ Reducing fever with antipyretics assumes that there is no diagnostic benefit of allowing the fever to persist.
- ▶ However Identification of certain fevers with different patterns is helpful diagnostically.

Need for pyrexia treatment

- ▶ Significant reduction in VO_2 (the rate of oxygen consumption) and VCO_2 (the rate of carbon dioxide elimination) during cooling.
- ▶ In patients with acute brain injury, pyrexia increase intracranial pressure and worsen secondary ischemic damage.
- ▶ In septic shock, temperature lowering by ibuprofen is associated with increased lactate clearance.

Post operative pain

Introduction

- ▶ Postoperative pain is a major challenge in patients undergoing surgery.
- ▶ Effective treatment of postoperative pain by multimodal approach is important
- ▶ As pain causes neuroendocrine stress responses and other harmful effects such as autonomic reflexes , adverse effects on organ function ,reflex muscle spasm
- ▶ In children it can cause long-lasting behavioral changes.
- ▶ Commonly used drugs to reduce postoperative pain following surgery include opioid, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol.

Post operative pain

- ▶ Surgery is life-saving is associated with potential harm, which frequently includes pain during and after the procedure.
- ▶ Inadequately controlled postoperative pain continues to be a widespread unresolved health-care problem.
- ▶ Increased awareness of the prevalence of postsurgical pain, advances in pain-management approaches are aimed at improving pain-related outcomes in recent decades,
- ▶ To prevent the progression from acute to chronic postoperative pain, more aggressive analgesic/anesthetic measures are needed to reduce the incidence of pain during and immediately after surgery.

Factors affecting post operative pain

- ▶ Location , type, and duration of the surgical procedure
- ▶ Type and extent of the incision and surgical trauma
- ▶ Physical and mental state of the patient including the patient's personal approach to pain
- ▶ Preoperative psychological and pharmacological preparation
- ▶ Type of anesthesia
- ▶ Pain management before and after the surgical procedure
- ▶ Incidence of surgical complications
- ▶ Quality of postoperative care

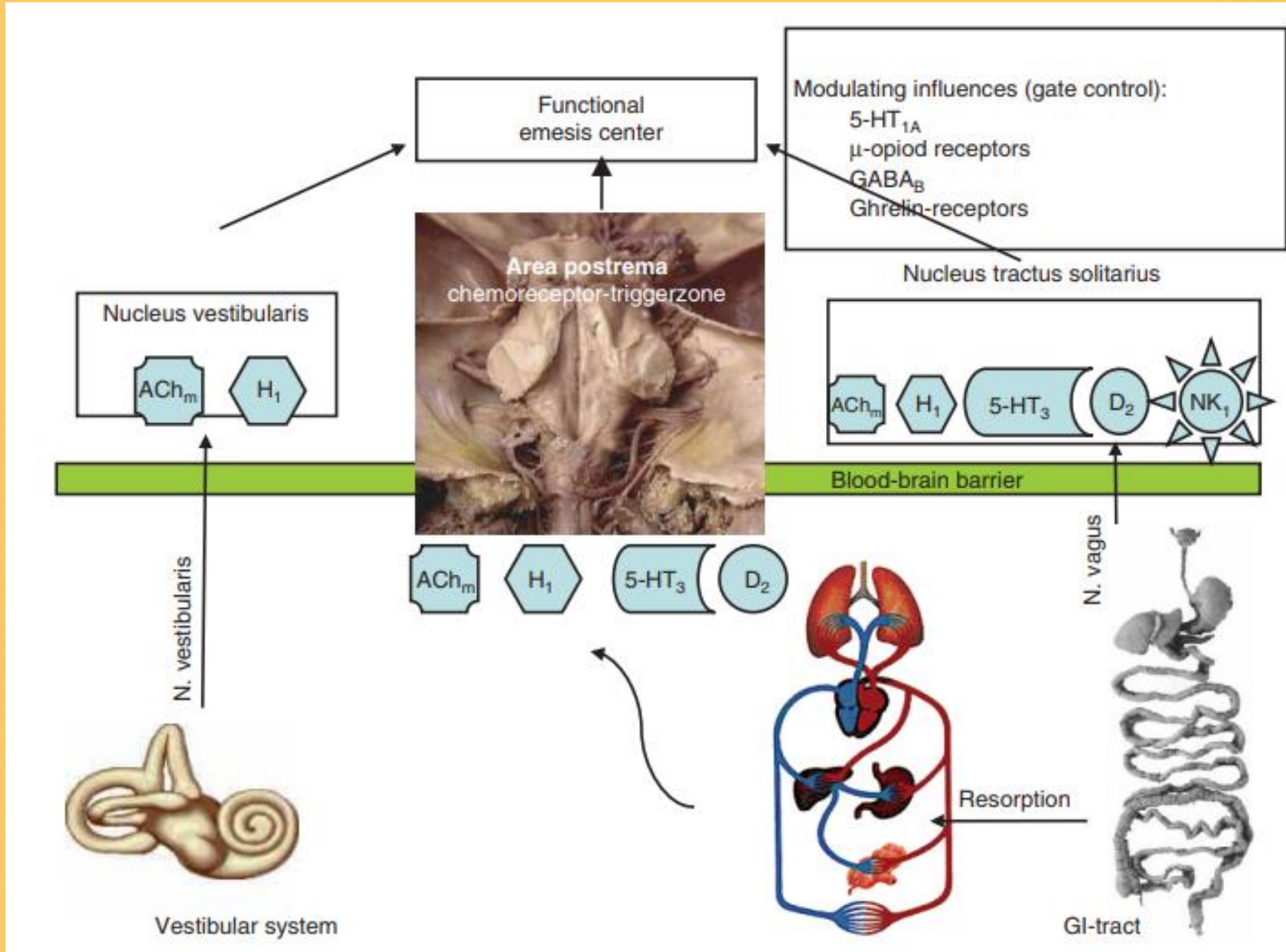
Consequences of sub optimal acute pain management

- ▶ Increased morbidity
- ▶ Impaired physical function and quality of life
- ▶ Slowed recovery
- ▶ Prolonged opioid use during and after hospitalization
- ▶ Increased cost of care.
- ▶ Early postoperative pain appears trigger persistent pain that may last for months after surgery in a substantial proportion of patients.

Post operative nausea and vomiting

- ▶ Nausea, vomiting, and retching frequently complicate recovery from anesthesia.
- ▶ Postoperative nausea and vomiting (PONV) is a patient-important outcome.
- ▶ Patients often rate PONV as worse than postoperative pain
- ▶ PONV usually resolves or is treated without sequelae, but may require unanticipated hospital admission and delay discharge
- ▶ In addition, vomiting or retching can result in wound dehiscence, esophageal rupture, aspiration, dehydration, increased intracranial pressure, and pneumothorax.

Pathophysiology of postoperative nausea and



Opioids and inhalation anesthetics cause nausea and vomiting by stimulation of the area postrema at the base of the fourth ventricle in the medulla.

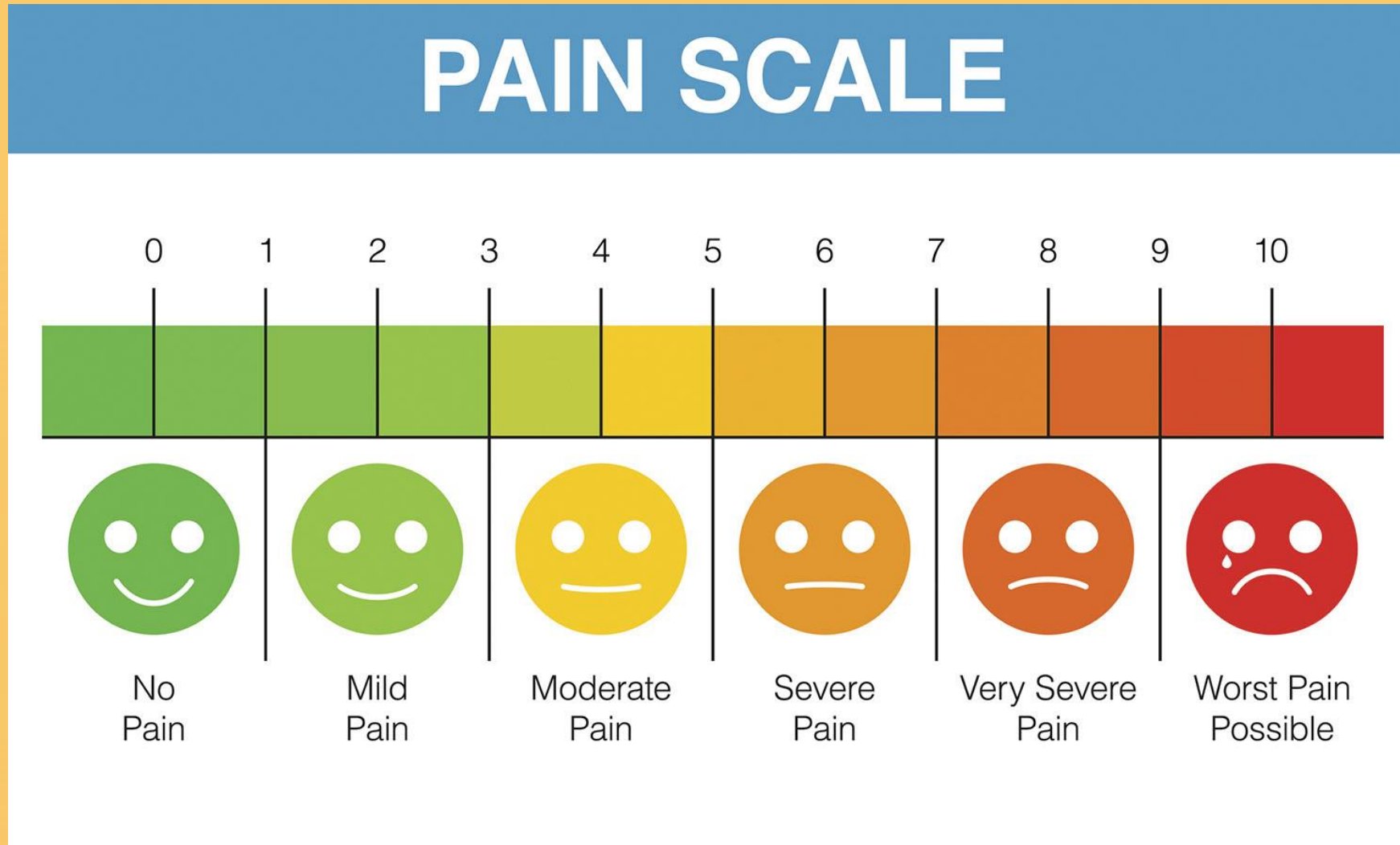
The area postrema then communicates with the central pattern generator via dopamine and serotonin to trigger the vomiting reflex



“Scales for measuring pain

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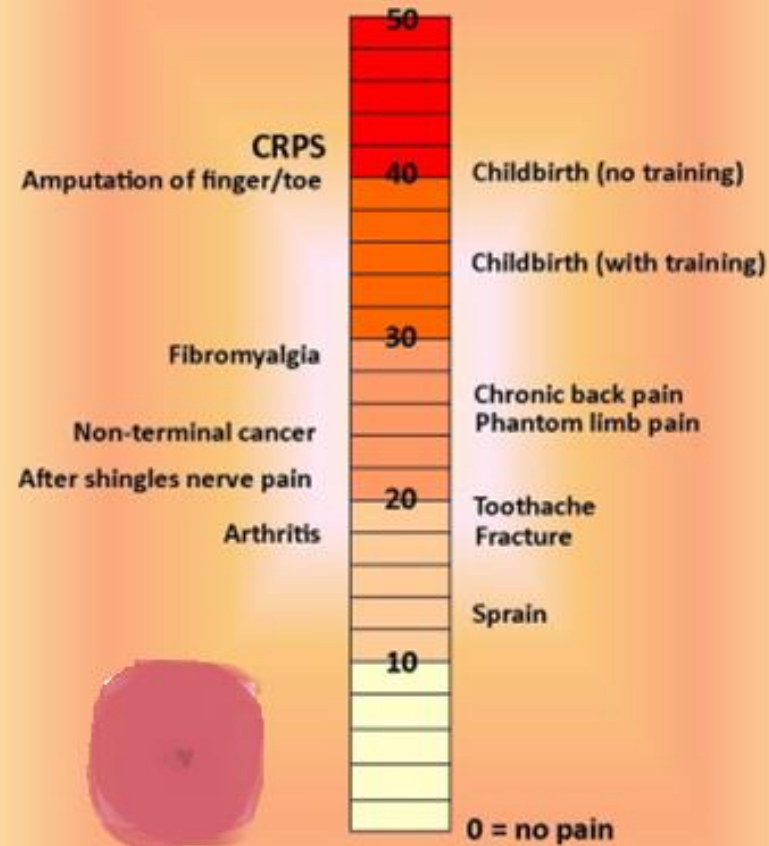
Visual analogue scale



Mac gill pain index

The McGill Pain Index

elleandtheautognome.wordpress.com



Rigorously tested scientific pain scale.

Overall score is determined by compiling various numerical and cross-referenced descriptive words, allowing direct comparison across conditions.

Management of post operative pain

- ▶ Opioids are considered as the primary analgesic therapy in moderate to severe postoperative pain.
- ▶ But opioids do not provide optimum patient satisfaction due to adverse effects such as sedation, respiratory depression, postoperative nausea and vomiting, hypotension
- ▶ NSAIDs are associated with many adverse effects such as gastrointestinal injury, increased operative site bleeding, renal toxicity, and bronchoconstriction.
- ▶ Paracetamol has a high safety profile in recommended dosage, lack of allergic potential and absence of contraindications in peptic ulcer diseases, hemostatic disorders, or pulmonary dysfunction opts to be a better analgesic.

Side effects of opioids post surgery

- Opioids cause nausea and vomiting by stimulation of the area postrema at the base of the fourth ventricle in the medulla.
- The area postrema then communicates with the central pattern generator via dopamine and serotonin to trigger the vomiting reflex
- Exacerbation of hypotensive effects of sedative-hypnotics (eg, propofol).
- Hypoventilation, respiratory depression and/or apnea.
- Chest wall and skeletal muscle rigidity, makes ventilation difficult.
- Increased intracranial pressure if hypercarbia occurs due to hypoventilation.

Feinleib J et al. In : Up to Date, Inc 2017. Wolters Kluwer. Updated on june 12,2019.
Accessed on 04-09-19

Casserly E et al. UpToDate. Link: <https://www.uptodate.com/contents/perioperative-uses-of-intravenous-opioids-in-adults>. 2017.

Side effects of opioids post surgery

- ▶ Bradycardia, which may be severe with high doses of opioids.
- ▶ Delayed postoperative emergence or delirium.
- ▶ Postoperative nausea and vomiting (PONV),
- ▶ Postoperative urinary retention, Postoperative ileus and constipation.
- ▶ Potential for development of acute tolerance or opioid-induced hyperalgesia.

Need of better and well tolerated analgesia

- ▶ There is a need for methodology of pain control which utilizes non-opioid medications which target different pain receptors to better manage and control pain.
- ▶ The synergistic effect of the multiple medications reduces the amount of opioid needed to control pain postoperatively, as opposed to using an opioid mono-therapy.
- ▶ Multimodal analgesia is a type of analgesia which uses multiple analgesics, adjunctive therapy with similar outcomes to those of opioid use.

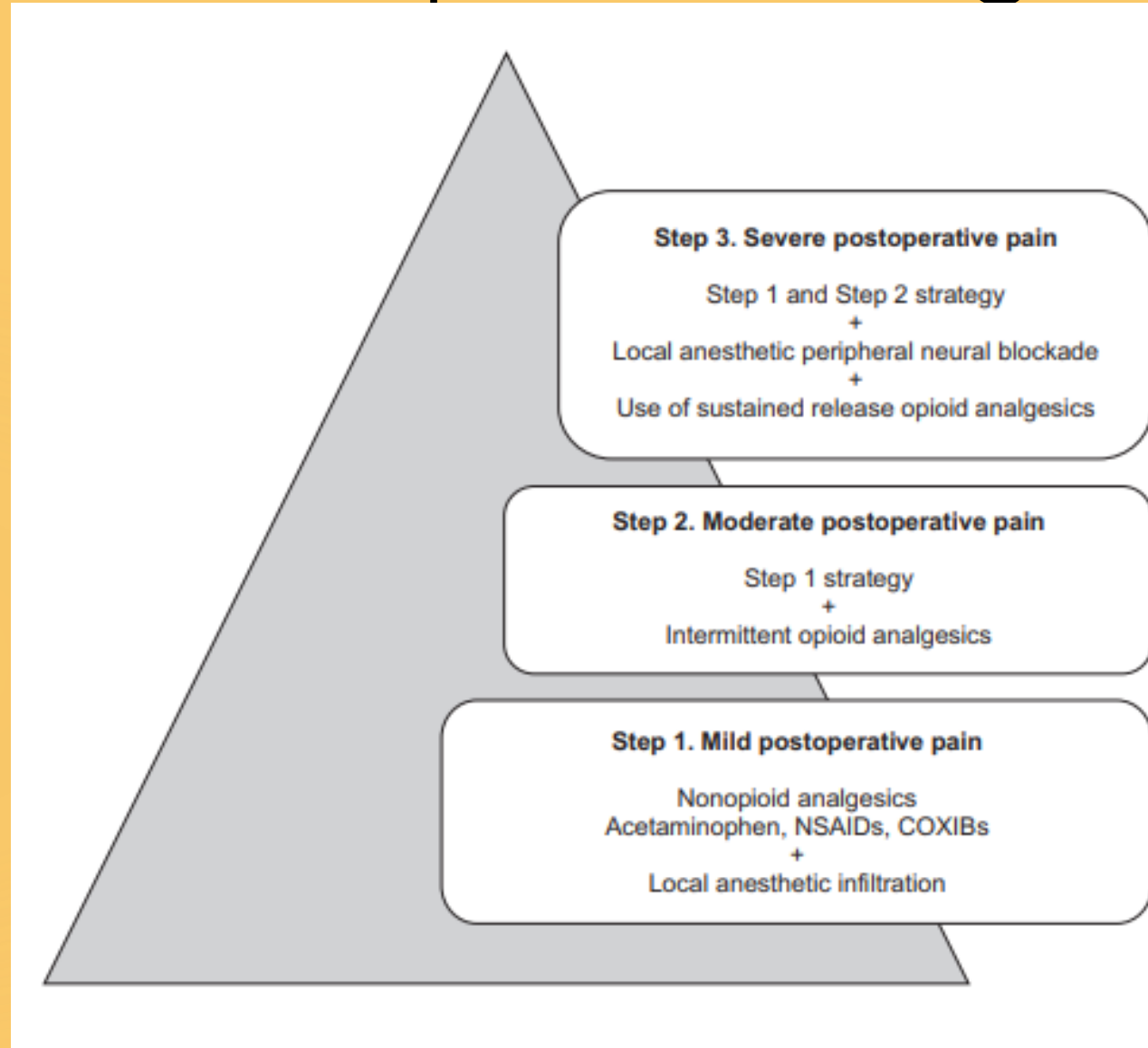
Multimodal analgesia

- ▶ Multimodal analgesia a concept first articulated by Kehlet and Dahl is the foundation for the management of acute postoperative pain.
- ▶ Principle : Combining analgesics with different modes or sites of action
- ▶ Advantages
 1. Improve analgesia
 2. **Reduce opioid requirements (“opioid-sparing” effect)**, and thereby reduces the adverse effects of opioids.
 3. Reduce complications
 4. Speed up recovery
 5. Possibly even reduce hospital cost.

New paradigm in analgesia manage



The ladder of therapy for multimodal postoperative pain management



Pharmacological components of Multimodal analgesia



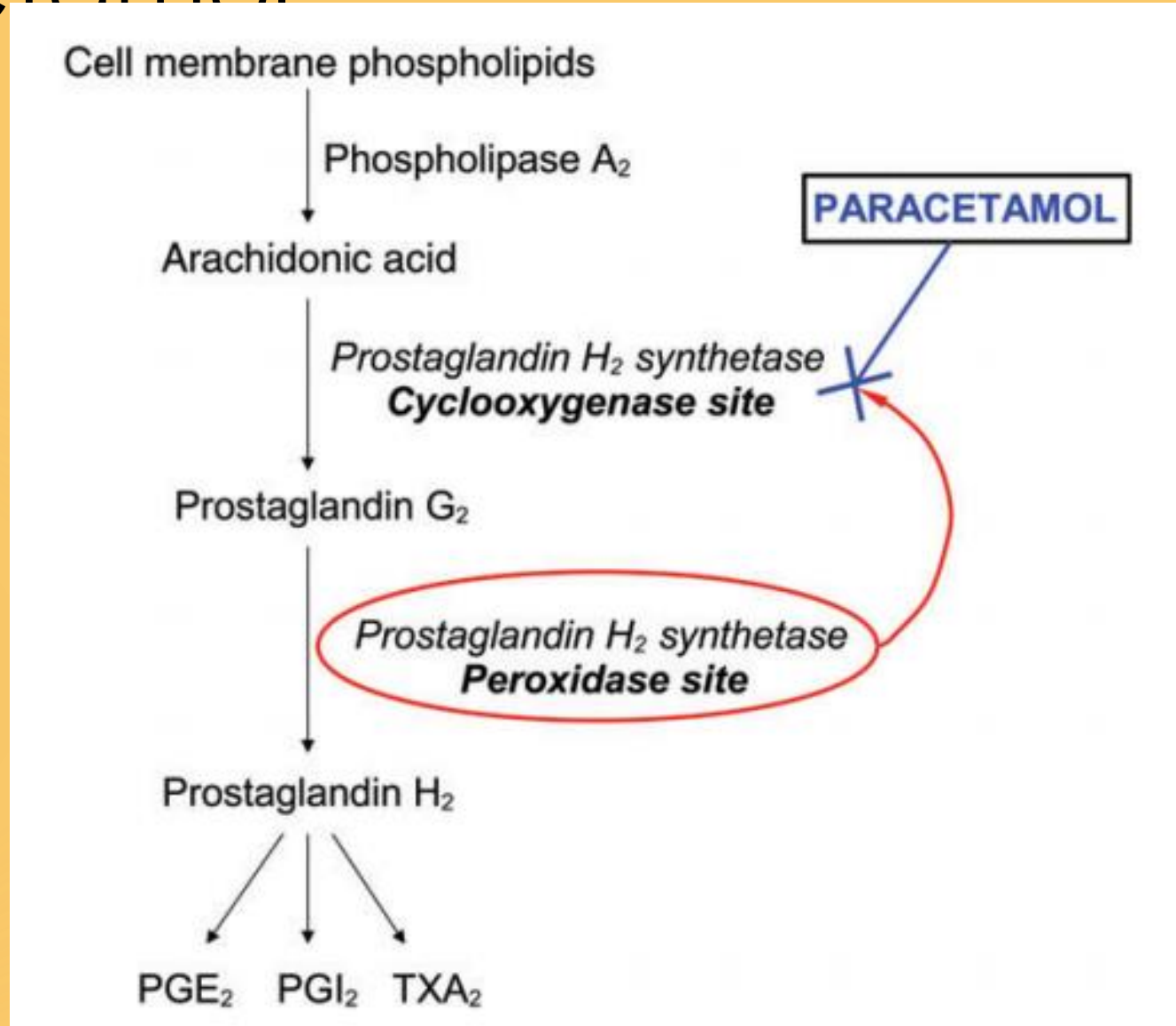
	Type	Examples
Principle	Regional anesthesia	Central neuraxial or peripheral nerve block Single-shot or continuous catheter +/- local infiltration analgesia
	Opioid analgesics Systemic nonopioid analgesics	Oxycodone, morphine, fentanyl, hydromorphone Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs)
Adjuvants	Gabapentinoids	Gabapentin, pregabalin
	N-methyl D-aspartate (NMDA) receptor antagonists Alpha-2 adrenergic agents Glucocorticoids Others	Ketamine, memantidine, dextromethorphan, magnesium Clonidine Dexamethasone Antidepressant, calcitonin, nicotine, capsaicin, cannabinoid, lidocaine

Intravenous Paracetamol

Description

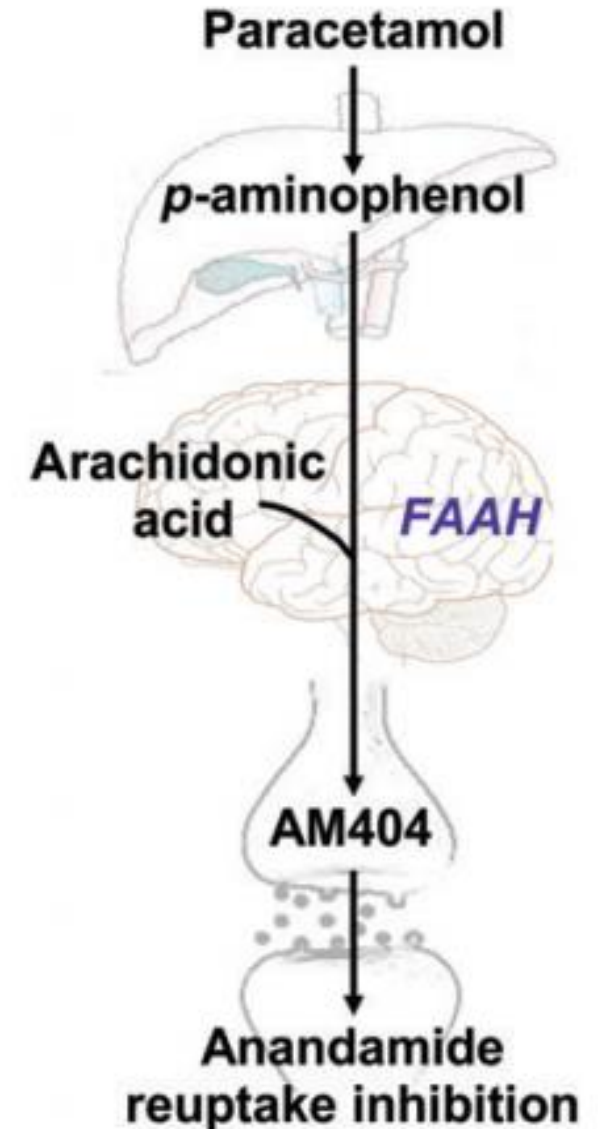
- ▶ First-line treatment for pain and pyrexia
- ▶ Plays an important role in multimodal analgesia.
- ▶ Possess a generally excellent safety profile except in significant overdose, with fewer drug interactions.
- ▶ Intravenous Paracetamol has faster onset of action, has cemented its position within virtually every anaesthetic/ peroperative pain management plan.
- ▶ The onset of analgesia after i.v. paracetamol occurs within 5 min, peaking at 40–60 min, and lasting 4–6 h.

Mechanism of action of Paracetamol



Endocannabinoid enhancement mechanism

- ▶ Fatty acid amide hydrolase (FAAH), an enzyme found predominantly in CNS
- ▶ In the presence of FAAH, paracetamol is conjugated with arachidonic acid to form the active metabolite, N-arachidonoylphenolamine (AM404).
- ▶ AM404 inhibits the reuptake of the endocannabinoid, anandamide, from synaptic clefts, increasing cannabinoid receptor activation on the post-synaptic membrane.
- ▶ Also activates activate descending serotonergic inhibitory pain pathway



Advantages of Intravenous Paracetamol

- ▶ Faster onset of analgesia
- ▶ Predictable pharmacokinetic and pharmacodynamics
- ▶ Avoidance of first-pass hepatic exposure through the portal circulation, which reduce the potential for hepatic injury.
- ▶ Lack of allergic potential
- ▶ Absence of contraindications in peptic ulcer diseases, hemostatic disorders, or pulmonary dysfunction.
- ▶ Additive effect on concomitant administration with opioids

Jibril F et al. Can J Hosp Pharm. 2015;68(3):238-47
Jebaraj B et al. Pain research and treatment. 2013;2013: 1:6.
Wick EC et al. JAMA Surg.2017 ;152(7):691-697.

Dosage of Intravenous Paracetamol from US FDA

Age Group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by any routes)
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1,000 mg	1,000 mg	4,000 mg in 24 hours
Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3,750 mg)
Age Group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by any routes)
Children 2 to 12 years of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3,750 mg)

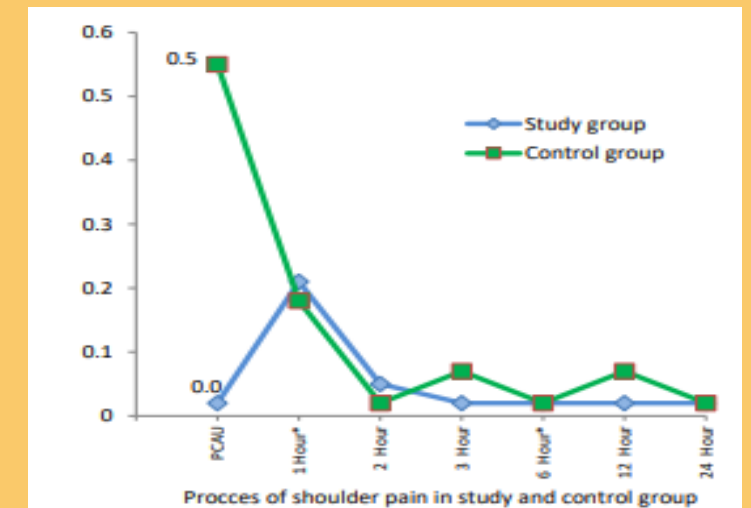
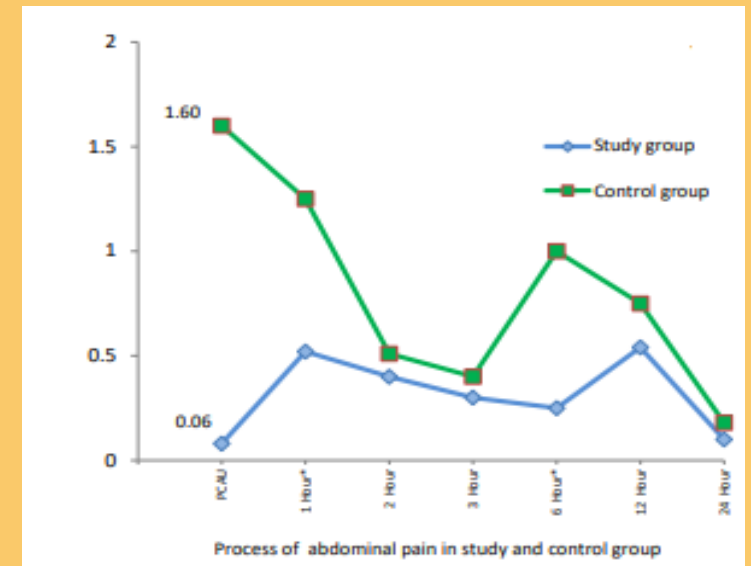
Clinical trials

Efficacy of different doses of Paracetamol in reducing pain post Gynaecologic Laparoscopy

- ▶ **Methods:** A double blind study was conducted on 92 women randomly assigned into two groups: paracetamol 2 g (study) (n=46) and 1 g (control) (n=46) into 100 ml normal saline, infused over 15 minutes at the end of surgery.

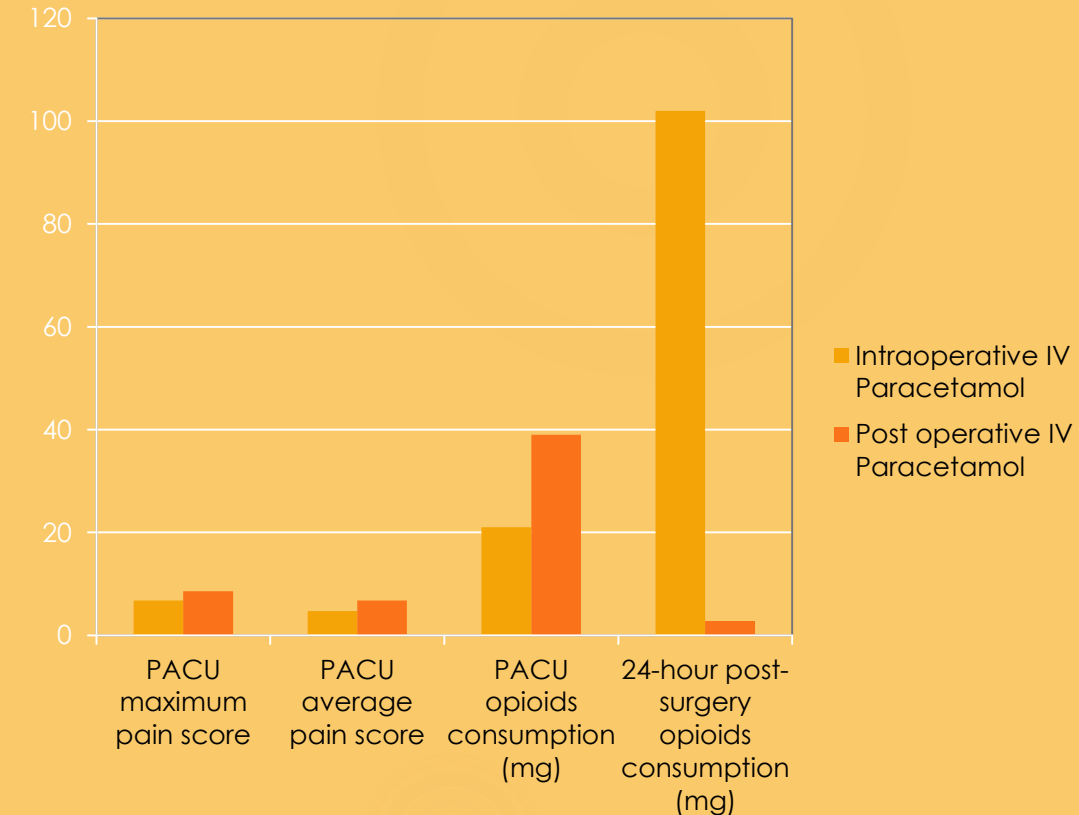
Abdominal and shoulder pain scores were recorded in post-anesthesia care unit (PACU), 1, 2, 3, 6, 12, and 24 hours after the operation.

- ▶ **Results:** Abdominal pain score and shoulder pain scores were less in study group compared to control group.
- ▶ **Conclusion:** Paracetamol in dose of 2 gram provides better and long lasting analgesic effect compared to 1 gram in treating post operative pain.



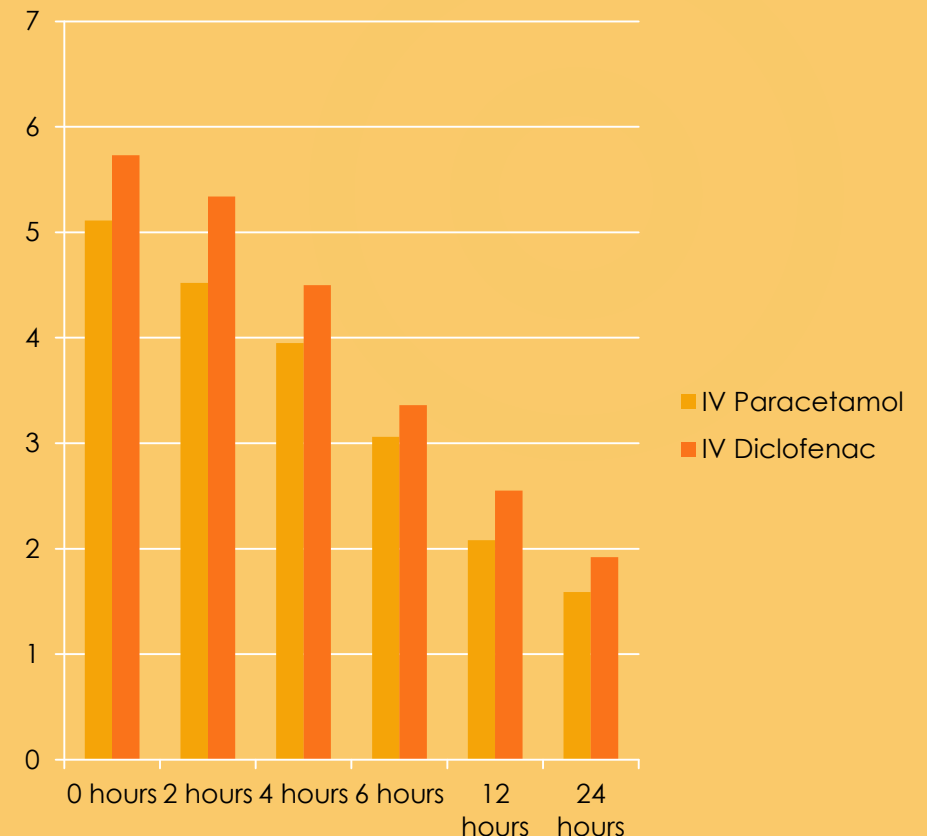
Effect of Paracetamol on intra operative and post operative pain, opioid consumption

- ▶ **Methods:** 147 patients who underwent abdominal or orthopedic spinal surgery.
- ▶ 41 patients received IV acetaminophen intraoperatively, 52 patients received it postoperatively and 54 control patients who did not receive IV acetaminophen.
- ▶ Patient outcomes were measured through 24-hour Visual Analog Scale (VAS) for pain scores, 24-hour opioid consumption, post-anesthesia care unit (PACU) pain scores.
- ▶ **Results:** Intraoperatively treated patients with IV acetaminophen group had a) significantly decreased 24-hour average pain scores compared to the postoperative IV acetaminophen group and to the control group ($p < 0.05$).
- ▶ **Conclusion:** Intraoperative Paracetamol controlled pain better than Post operative Paracetamol administration, reduced the requirement of Opioids.



Effect of Intravenous Paracetamol and Diclofenac in Laparoscopic cholecystectomy

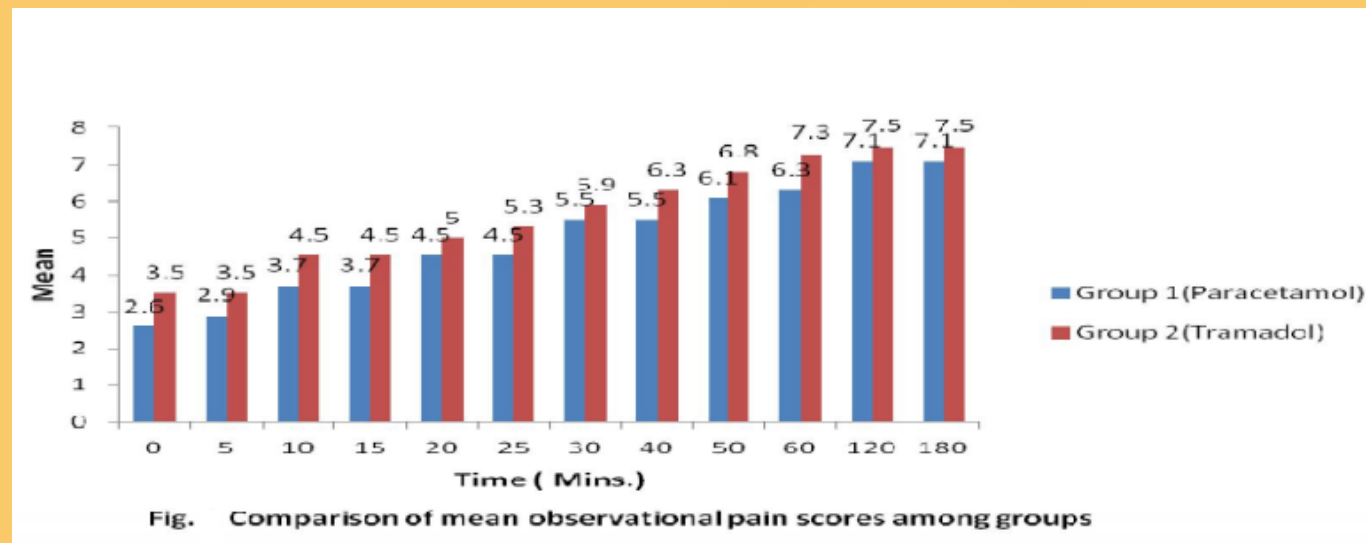
- ▶ **Methods:** 128 patients were included , were divided into two groups.
- ▶ The first group received 15mg/kg (maximum 1gm) intravenous paracetamol and the second group received 2mg/kg (maximum 75mg) intravenous diclofenac 30 minutes prior to ending of surgery.
- ▶ A questionnaire was responded by patients and chart was maintained by visual analogue scale
- ▶ **Results:** Most of the patients in paracetamol group had low mean pain scores in post-operative period and provided an extended analgesia compared to diclofenac.
- ▶ No serious postoperative complication was observed in paracetamol group.



- ▶ **Conclusion:** Intravenous paracetamol provided better and prolonged analgesia compared to Diclofenac with lesser side effects

Comparison of IV Tramadol and IV paracetamol in post operative pain

- ▶ **Methods:** 40 patients aged 15-40 years were enrolled in the study.
- ▶ patients were randomized into two groups. Group 1 [n=20] received 15mg/kg of IV paracetamol and group 2 [n=20] received 1.0 mg/kg of IV tramadol over 15 minutes.
- ▶ Pain scores were recorded.
- ▶ **Results:** Group treated with IV Paracetamol showed better improvement compared to IV Tramadol ($p < 0.05$).
- ▶ **Conclusion:** Paracetamol is more effective than Tramadol in post operative pain



Summary

- ▶ IV acetaminophen has gained popularity for inpatient management of acute pain for its practical and clinical advantages.
- ▶ IV administration is associated with more predictable pharmacokinetics compared with rectal (30%-40% bioavailability) and oral acetaminophen (60%-70% bioavailability).
- ▶ Predictable kinetics, ease of IV administration has made it an especially attractive option in the critically ill, a population with altered gut absorption.
- ▶ IV acetaminophen has shown promise in improving patient satisfaction, managing fever, and decreasing postoperative opioid requirements.
- ▶ These features have made it one of the most widely used medications in treating post operative pain.