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The Sri Lanka Prescriber

Acute Pain Management during the Perioperative Period

Introduction

According to the International Association of the Study of Pain (IASP), pain has been defined as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," and is expanded upon by the addition of six key note (Revised definition 2020).

Pain is subjective and has an emotional and a psychological component. Therefore, pain thresholds vary among individuals. Factors such as social, cultural, gender and age can influence patients' perception of pain (1). Therefore, when treating postoperative pain, it should be patient-centred, as one size does not fit all individuals alike (2). Pain can remain a hidden entity and clinicians need to look for it during the postoperative period. If unidentified, it could lead to devastating consequences to the patient and incur an increased cost to the institution due to a longer hospital stay. Evaluation of pain should be included in daily patient assessment during the perioperative period. A narrative review reports that approximately 20% of postoperative patients complain of severe pain (3). Identifying and alleviating pain remains a core responsibility of healthcare providers (4).

The degree of pain will differ depending upon the surgical procedure. Upper abdominal and thoracic surgeries are more painful when compared to lower abdominal surgery (5). Joint replacement surgeries can present with severe postoperative pain (6). Surgical techniques such as laparoscopic procedures and horizontal skin incisions during open surgery can minimize postoperative pain (7).

A shift in the trend towards enhanced recovery after surgery (ERAS) has led to a reduction in opioid consumption by employing multi-modal analgesic techniques to provide postoperative pain relief (7). This has an important bearing on opioid misuse which has become a problem in the recent past in western countries (8,9), though not so much of a problem in Sri Lanka.

Acute pain, by definition, lasts for seven days from the initial insult and becomes chronic if not recognized and treated early in the postoperative period.1 Pain which extends beyond three months after the initial injury is defined as chronic and can be difficult to treat (1, 10).

The aim of this article is to provide an overview of consequences, assessment, planning and management of acute perioperative pain in adult patients presenting for surgery and methods used to improve outcomes in the postoperative period.

Aims of perioperative pain management

Main aim of treating postoperative pain is to ensure early recovery and mobilization (7). This will improve patient satisfaction. Treating acute pain can prevent development of chronic pain which can be debilitating to the patient.

Persistent postoperative pain can result in longer hospital stay, excessive utilization of resources and an increased cost to the health sector (11). Therefore, assessing, recognizing and treating acute perioperative pain can improve heath related quality of life for the patient and effective utilization of resources.

Consequences of acute perioperative pain

Consequences of poorly managed pain affects most systems in the body due to activation of the sympathetic nervous system. (Table 1)

Table 1: Consequences of pain

System	Effects
Cardiovascular	Increased heart rate and blood pressure Increased myocardial oxygen demand Induce a supply-demand imbalance which can precipitate myocardial ischaemia in susceptible individuals
Respiratory	Shallow breathing leading to basal alveolar collapse/atelectasis Hypoxia, hypercarbia Poor cough, poor compliance with chest physiotherapy leading to retention of sputum and subsequently pneumonia
Gastrointestinal	Impaired gastric motility leading to constipation
Musculoskeletal	Increased catabolic demands Poor wound healing and muscle weakness Delayed mobilization which can predispose to deep vein thrombosis
Central nervous system	Psychological stress Anxiety, poor sleep Neuroplasticity, peripheral and central sensitization finally leading to chronic pain

Recognize, Assess and Treat: "RAT" approach

The Essential Pain Management (EPM) course, an initiative of the Faculty of Pain Medicine in collaboration with the Australian and New Zealand College of Anaesthetists (ANZCA) uses a simple approach to managing perioperative pain.

- **Recognition**

Recognition of pain should not be confined to the postoperative period. Meticulous preoperative planning and preparation can help clinicians detect patients who are more likely to develop severe postoperative pain and act upon it immediately. During the preoperative evaluation it is important to determine the severity of pain depending upon the type of surgery. It is also important to obtain a detailed history regarding medical co-morbidities, allergies, and substance use (2,12). Involving the patient as part of shared decision making will enable the clinician to discuss the benefits versus risk of the available methods and determine patient's preference (2,12). Past experience of pain should also be considered during the decision making process.

During the postoperative period a detailed history should be followed by a clinical examination focused on objective measurements such as vital signs. However, it is important to remember that objective assessment alone is not sufficient to recognize pain as they may not always be reliable and valid.2 Self-reported pain and behavioural observations can also give cues to the clinician, but they must be interpreted with caution (2). Recognition of pain in patients with poor cognition, learning difficulties and those under the influence of sedatives can be challenging (2,3). Involvement of care-givers can be beneficial in certain circumstances (2).

- **Assessment**

Assessment of pain should include a detailed description related to onset, nature, intensity, duration, radiation, aggravating and relieving factors. This will help to determine if dosing of drugs is adequate, if changes or additional interventions are required or input from an acute pain team and pain consultant is warranted (2). Self-reporting on pain should be supplemented by validated pain intensity assessment scales to quantify the degree of pain (2).

Commonly used tools include the numerical rating scale (13) (Figure 1), verbal rating scale (VRS) and visual analogue scale (VAS). Selection of a particular tool will depend on a number of factors. Level of cognition, literacy, consciousness, language and cultural barriers will need to be considered when selecting a particular scale for a patient (2). Currently there is no evidence to recommend one tool over another on postoperative pain related outcomes. These unidimensional scales may not be able to express patients experience such as tolerance to pain and functional recovery (3).

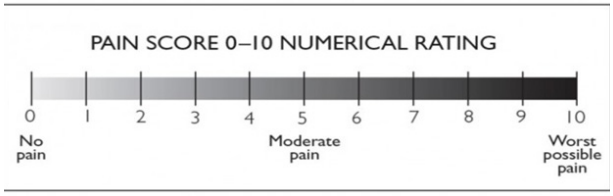

Figure 1: Numerical Rating Scale: NRS *(downloaded from www.physio-pedia.com/Numeric_Pain_Rating_Scale)*

NRS (Figure 1) is easy to administer and is valid (14). It is one of the most commonly used scales during the postoperative period. VRS utilizes words to categorise pain (14). Expressions used include none, mild moderate and severe. It is a simple tool and can be used with ease and is valid in terms of intensity of pain. Language barrier is a limiting factor. It is less precise and sensitive when compared to a visual analogue scale (14).

VAS consist of a 100mm unmarked line. Standardized words such as no pain is marked on the extreme left of the line and worst pain marked on the right. Patient is advised to place a mark on the line indicating the intensity of pain (14). Patient's level of understanding will affect the final

result when using such scales and this can be a limiting factor.

Trends in scores of pain assessment scales are more important than a single score.3 Re-assessment of pain using such scales is important. Interval of re-assessment will vary depending on a number of factors. Following administration of parenteral medication, it may require 15-30 minutes to bring about a change, whereas with oral medication the duration will be longer (2).

- **Treatment of perioperative pain**

Poorly managed post-surgical pain is a predictor of a less well appreciated entity termed "chronic post-surgical pain" (CPSP). It is also referred to as persistent post-surgical pain (PPSP). CPSP/ PPSP by definition is pain after surgery, lasting longer than the expected period of healing and occurs in 10-65% of post-surgical patients (15,16).

Pre-emptive analgesia is defined as an analgesic intervention initiated before the noxious stimulus in order to block the central or peripheral transmission of pain (17). Preventive analgesia is functionally defined as an attempt to block pain transmission prior to injury, during the noxious stimulus and after injury, extending throughout the recovery period (17).

Maximum clinical benefit is observed when there is blockade of pain during the perioperative period. A multi-modal approach can optimize perioperative analgesia.

Pain management begins preoperatively with an assessment and development of a plan of care tailored to the individual patient and the surgical procedure. Patient education plays a pivotal role in successful pain management (2,13). Goals of pain therapy should be targeted to improve perioperative outcomes and ambulation rather than attempting to achieve a specific pain score.

Multimodal Approach

Multimodal approach to pain management refers to using a variety of analgesic methods that have different mechanisms of action acting at different sites of the pain pathway. This is a superior technique when compared to using a single agent. This method maximizes the analgesic effect while lowering the incidence of side effects. An understanding of pain physiology is useful to appreciate the site/s of action of drugs, though it is beyond the scope of this article to discuss it in detail. The diagram below illustrates the pain pathway with the site/s of action of drugs and various techniques. (Figure 2)

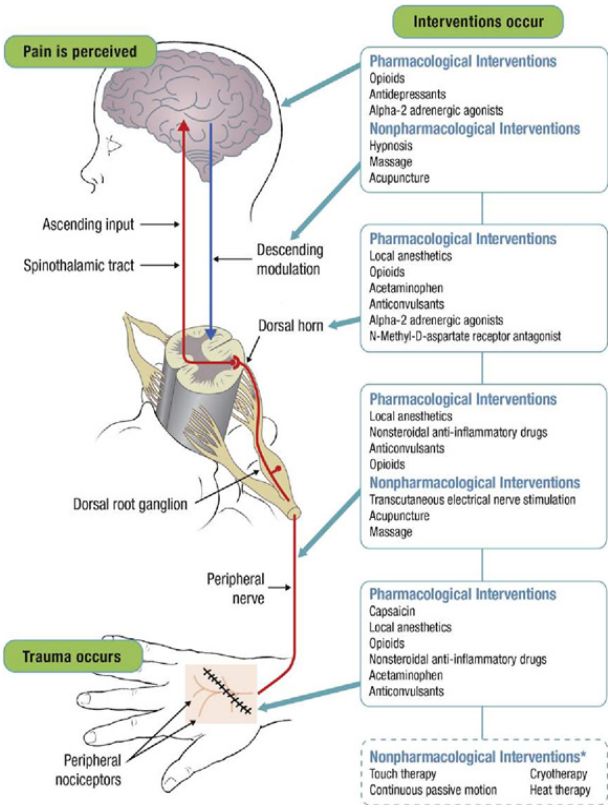

Figure 2: Pain pathway illustrating the site of action of intervention/s
(Adapted from: R Manoworren, 2015, AORN Journal, 101(3):307-318)

Multimodal pain management includes pharmacological as well as non-pharmacological measures. Use of non-pharmacological methods are less well recognized in acute pain management. However, these techniques have shown to have beneficial effects when used together with pharmacological agents. Non-pharmacological methods include, patient education, nursing care, positioning (e.g. elevation of an affected limb), application of cold or heat, Transcutaneous Electrical Nerve Stimulation (TENS), and various behavioral modalities such as mirror therapy, relaxation, mindfulness and meditation (13).

WHO analgesic ladder (Figure 3) was presented by the World Health Organization in 1986 to use as a framework to treat cancer pain. The increasing intensity of cancer pain with disease progression signifies the upward trend of steps of this ladder. Since postoperative pain tends to decrease in intensity with time the WHO analgesic ladder is used in reverse order in that setting.

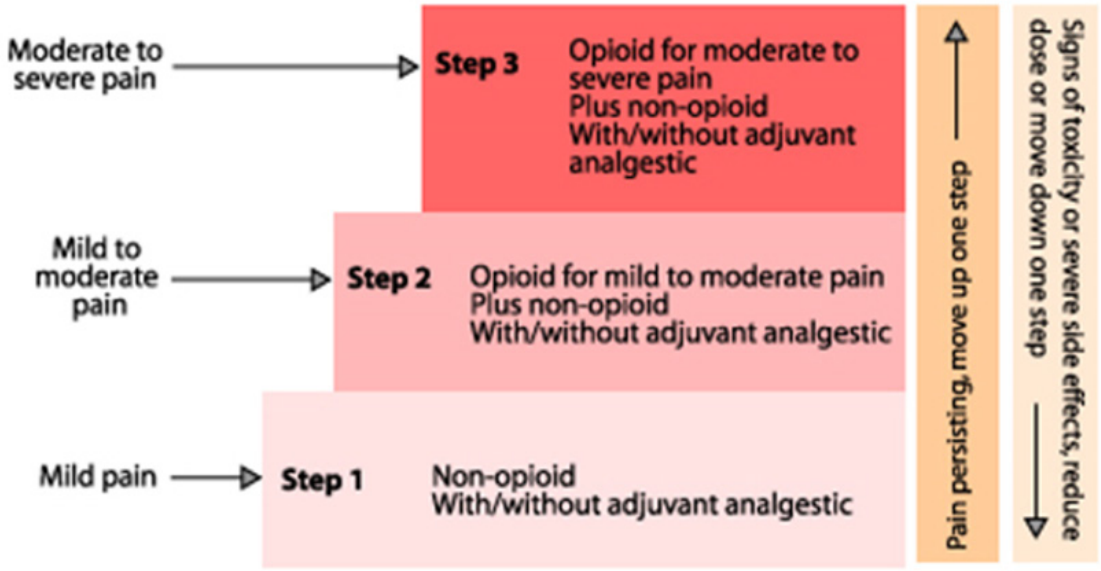

Figure 3: WHO Analgesic Ladder (Source: Anaesthesia UK https://www.anaesthesiauk.com)

As the intensity of pain is high following surgery, the analgesic plan should start before surgery and continue throughout the intraoperative and postoperative period. Opioid sparing techniques such as regional and local anaesthetic techniques should be used whenever possible.

increased risk compared to other less invasive techniques. However, such techniques can be beneficial in major thoracic and abdominal surgery. Postoperative cardiac and pulmonary complications are not an uncommon finding following this type of major surgery (2).

Patient Controlled Analgesia (PCA) can be used with an epidural whereas spinal analgesia is often limited to a single injection. PCA provide superior pain relief compared to continuous infusions.

Truncal blocks are performed by placing a large volume of local anaesthetic in a fascial plane. Transversus Abdominis Plane (TAP) block is commonly used for abdominal surgery, mostly in colorectal surgery. Quadratus Lumborum block and rectus sheath blocks are gaining wide-spread popularity. These blocks are performed under ultrasound guidance. Local anaesthetics are administered either as a single injection or by placing a catheter for continuous infusion (7).

Drugs

Drug therapy includes simple analgesics, opioids and adjuvants. Adjuvants are agents that are used primarily for various other purposes but can also be used as analgesics when required. (Table 2)

Table 2: Non- Opioid Analgesics

Drug	Comments
Paracetamol	Can be administered intravenously, orally and rectally. Can be started preoperatively and prescribed for regular use in the initial postoperative period. Has opioid sparing effect when used with NSAIDs for moderate to severe pain (8).
NSAIDs	e.g., Diclofenac sodium – up to 150 mg/day oral/rectal Combine with proton pump inhibitors to minimize gastrointestinal side effects. Potential risk for increased cardiovascular events. Monitor renal function and avoid in patients with potential renal impairment, hypovolemia or hypotension Has opioid sparing effect when used with paracetamol for moderate to severe pain (8)
Gabapentin Pregabalin	Useful adjuvant. In Enhanced Recovery After Surgery (ERAS) pathway: it is given 1-2 hours preoperatively (Gabapentin 600-1200 mg and Pregabalin 150-300 mg) and continued postoperatively (Gabapentin 600 mg single or multiple doses or Pregabalin 150 - 300 mg after 12 hours) (2). Benefits may be offset by increased postoperative sedation, dizziness and visual disturbance
Lignocaine	Intraoperative use reduces postoperative pain scores. Caution in liver disease and heart failure. Lignocaine toxicity is of concern. Look for light headedness, dizziness, visual disturbance and rarely dysrhythmias (7).
Ketamine	Used intravenously and sublingually Seek advice from a pain specialist or a consultant anesthetist for the dosing regime

Opioids

Opioids are administered via many routes, namely oral, transdermal, subcutaneous, intravenous, neuraxial & rectal. Combinations of opioids should be avoided. The side effects of opioids which limits their use are respiratory depression, nausea, vomiting, pruritus and reduced bowel motility causing ileus and constipation. Long term use can lead to dependance and addiction.

Using PCA can minimize the total dose of opioids used as well as give the patient confidence and satisfaction of being in control of his own pain management. Non-availability of PCA pumps is a limiting factor (17,19).

Opioid tolerant patients (due to prescription opioid use or substance abuse) presenting for surgery poses a challenge to the team. A multidisciplinary care plan needs to be formulated in order to ensure optimal perioperative analgesia while preventing persistent opioid use. This will enable smooth transition in to the pre operative status of opioid use (9,19).

Opioid tolerant patients should be managed to prevent opioid withdrawal. It is important to provide effective analgesia and they should not be denied opioids. Doctors must ensure that there is continuity of care in the community following hospital discharge (19).The commonly used opioids (17) and the doses are listed in Table 3.

Table 3: Commonly used opioids

Opioid	**Route**	**Comments**
Morphine	IV	Should be given in incremental doses while monitoring side effects
	IV PCA	Avoid background infusion in opioid naive patients
	SC	Absorption is variable
Codeine	Oral	Analgesia is due to conversion to morphine. Some patients lack the converting enzyme Available in combination with paracetamol in Sri Lanka
Fentanyl	IV	Fentanyl patches should not be used on opioid naive patients or for acute pain
Tramadol	oral	Extreme caution when used in combination with other opioids and sedatives

IV-intravenous; PCA-patient controlled analgesia; SC-subcutaneous;

During perioperative pain management, it is paramount to look for correctable causes of pain e.g., abscess, haematoma formation and infection. Timely detection and treatment of such causes could reduce the analgesic requirements.

Discharge planning

Patients should be evaluated for pain at the time of discharge. Analgesics should be prescribed together with a suitable plan incorporating non-pharmacological interventions such as physiotherapy to ensure early ambulation.

Case scenarios: How can we manage their perioperative pain?

Scenario 1

32-year -old male is scheduled to undergo a right inguinal hernia with mesh repair. He is fit and well with no known co-morbidities. He has no allergies. He is admitted to the surgical ward. He has consented to undergo the procedure under spinal anaesthesia.
How can we provide optimal pain relief for him?

Preoperative period: administer pre-emptive analgesia with 1g of paracetamol orally 2 hours prior to surgery

Administer diclofenac suppository 1mg/kg per dose just prior to the procedure in theatre (following administration of the subarachnoid block to reduce discomfort during insertion of suppository)

Administer prophylactic antibiotic 30-60 minutes prior to the procedure (as a mesh is to be used for repair) to avoid postoperative complications such as infection which could further contribute to pain.

Intra-operative period: Subarachnoid block (spinal anaesthesia) will provide dense anaesthesia as well as analgesia. Combination of 0.5% hyperbaric bupivacaine with a short acting opioid such as fentanyl will be used.

Postoperative period: Prescribe regular oral paracetamol and diclofenac suppository for 48 hours.
Ensure the two drugs are spaced appropriately so that the patient will have analgesia throughout the day.

Use pain assessment methods and re-assess.

Scenario 2

62-year-old lady is admitted for a laparoscopic cholecystectomy. She is diagnosed with type II diabetes for more than 10-years. She is on amitriptyline and gabapentin for neuropathic pain of her lower limbs. She has no allergies.

How can we manage her perioperative pain?

Preoperative period: continue amitriptyline and gabapentin.
Prescribe 1g of oral paracetamol as pre-emptive analgesia 2 hours prior to surgery

Intra-operative period: Prophylactic antibiotics 30-60 minutes prior to surgery

General anaesthesia (GA): Insert diclofenac suppository provided her renal parameters are normal.

Laparoscopic port sites will be infiltrated with local anaesthetic by the surgeon
Administer opioids at induction: a short acting opioid such as fentanyl (1-2 microgram/kg dose) followed by a long acting opioid such as morphine (0.1mg/kg/dose).

Single or combination of antiemetics (such as ondansetron alone or with dexamethasone) will be administered during surgery to prevent postoperative nausea and vomiting which could contribute to postoperative pain.

Ideally procedure to be done under low-pressure pneumoperitoneum and at the end of surgery to decompress trapped carbon dioxide which may contribute to referred shoulder tip pain secondary to diaphragmatic irritation.

Postoperative period: prescribe regular oral paracetamol in combination with diclofenac suppositories for 48 hours (provided no contra-indication) with regular antiemetics as laparoscopic surgery predisposes patients to postoperative nausea and vomiting.

Continue amitriptyline and gabapentin. Consider an additional analgesic if required for breakthrough pain according to the WHO pain ladder

Re-assess pain

Scenario 3

A 59-year-old male patient is scheduled for an elective laparotomy for a colonic malignancy. He is diagnosed with hypertension and bronchial asthma. He is allergic to diclofenac sodium.

How can we plan his perioperative pain management?

Preoperative period: consent for an epidural

Pre-emptive oral paracetamol, can consider oral gabapentin 300mg

Intra-operative period: Insert epidural before inducing anaesthesia

Intravenous low dose ketamine at induction (0.5mg/kg)

Intravenous long acting opioid (morphine) alone or with a short acting opioid (fentanyl) at induction

Commence intra-operative epidural infusion with low concentration bupivacaine

Intravenous antibiotics 30-60 minutes prior to skin incision

Intravenous antiemetics

Postoperative period: continue epidural bupivacaine infusion (with short acting opioid, fentanyl)
Prescribe regular oral paracetamol if patient can tolerate orals (if not intravenous paracetamol) 6 hourly

Re-assess pain. If required add sublingual ketamine 0.25mg/kg/dose 4-6 hourly. Regular doses of oral gabapentin. Antiemetics if needed. If patient refused an epidural, PCA can be offered using either morphine or fentanyl

Scenario 4:

A 32-year-old fit and well male patient weighing 60 kg is admitted following a motor cycle accident. He has an isolated injury to his right lower limb with a comminuted fracture of proximal tibia and fibula. He requires an above knee amputation as his limb is not salvageable.

How can we provide effective analgesia for him in the perioperative period?

Preoperative period: Assess pain and haemodynamic status. Aim to achieve optimal analgesia prior to surgery

Oral paracetamol 1g

Oral gabapentin 300 mg stat

Diclofenac sodium 50 - 100 mg (if no contra-indications) with omeprazole 20mg

Intravenous morphine 5mg stat and increments of 2.5 mg until pain is controlled (while monitoring): other options include either a morphine PCA or subcutaneous morphine 0.1-0.15mg/kg

Consider epidural analgesia with local anaesthetic alone or with fentanyl - continuous infusion or PCA. Repeat the drugs and maintain analgesia until surgery. Talk to the patient, reassure, discuss the availability of prosthetic limbs and address any fears he may have

Intra-operative period: If an epidural catheter has been sited preoperatively can use it to provide anaesthesia

If not, offer him spinal anaesthesia

Consider a surgically placed perineural catheter to continue local anaesthetic infusion of 0.125% - 0.25% bupivacaine postoperatively

Postoperative period: If already in place, continue epidural analgesia: continuous infusion or PCA with monitoring or continue perineural analgesia if a catheter is placed intra-operatively

Continue oral paracetamol, gabapentin and if appropriate NSAIDs

Inquire on phantom limb sensation or pain (PLP): Treatment includes mirror therapy. Effective perioperative analgesia is the best option to prevent PLP

Look for stump pain: Exclude infection, wound breakdown, arterial insufficiency (commoner with patients with having vascular disease), osteomyelitis, haematoma, bony spurs, insufficient covering of the stump, neuroma formation, heterotopic ossification and poorly fitting prosthesis.

Ketamine - low dose infusion (up to 15mg/hour). Bandaging of stump appropriately to enable fixation of a prosthesis. Stump exercises to strengthen stump muscles

Prevent back pain by advising on posture until prosthetic limb is fitted. Exclude any specific spinal or disc pathology. Treatment includes simple analgesics, antiinflammatory agents and use of trans electrical nerve stimulator (TENS).

Summary

Acute pain following surgery can have devastating consequences to the patient and if undetected can lead to chronic pain. Recognition is based on a focused history followed by examination. Several pain scales are available for quantification of pain. However, they are not without limitations.

Treatment of perioperative pain should commence in the preoperative period and extend in to the intra and postoperative period. Multimodal analgesic techniques provide better pain relief. Characteristics of pain varies depending upon the surgery. Therefore, procedure specific pain management protocols can be a useful tool to the clinician. Re-assessment of pain is important following any intervention.

Management of pain involves discussion of options, side effects, limitations and benefit versus risk with the patient and care-givers where appropriate.

Aim of acute perioperative pain management includes improvement in outcomes and early ambulation. Early recognition, assessment and treatment of acute perioperative pain can improve patient satisfaction and quality of life while effectively utilizing healthcare resources.

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Self- assessment questions

1. The following are consequences of unaddressed postoperative pain following thoraco-abdominal surgery
    a. Anxiety
    b. Constipation
    c. Hypoxia
    d. Myocardial ischaemia
    e. Urinary retention

2. Regarding assessment of pain
    a. Using a numerical rating scale (NRS) from 1 to 10 is very useful
    b. Detection of elevated blood pressure may indicate unrelieved pain as a likely cause following laparotomy
    c. It is important to assess intensity of pain at rest and during movement
    d. Visual analogue scale (VAS) is an ideal tool to be used in the elderly
    e. VAS are known to give reproducible results within the same individual

3. In the management of perioperative pain

a. Optimal management will minimize the development of persistent post-surgical pain
b. Use of several analgesic drugs that act on different sites of pain pathway is likely to cause more side effects
c. Non-pharmacological interventions are not effective in surgical pain management
d. WHO analgesic ladder is used in reverse order in the management of surgical pain
e. Mirror therapy is used in the management of phantom limb pain

4. When prescribing opioids during the perioperative period

a. It is common practice to use several opioids in one patient
b. Patient controlled analgesia is more likely to provide better pain relief than intermittent dosing
c. Codeine will produce effective analgesia in all patients
d. It is unlikely for morphine to cause addiction in an opioid naive patient when prescribed for one week
e. Nausea is uncommon with morphine

Self- assessment - Answers

1. TTTTT

All options are true as they are secondary to activation of the sympathetic nervous system.

2. FTTFT

Numerical rating scales extends from 0-10. High blood pressure is secondary to activation of the sympathetic nervous system. Pain should be assessed both at rest and on movement to detect the intensity. Elderly may have visual impairment therefore, VAS may not be the best option.

3. TFFTT

Goals of optimal pain management is to prevent the development of PPSP. Multimodal analgesia will result in better outcomes and less side effects. Non-pharmacological interventions when combined with drugs provide effective analgesia. Since post-surgical pain reduces in intensity with time the steps in the ladder are used in the reverse order. Mirror therapy is a behavioural modality used in PLP.

4. FTFTF

Drugs acting on the same receptor should be avoided. PCA empowers the patient with the task of administering the drug by himself. It can also be given as a continuous infusion. Therefore, it provides better pain relief. Some individuals lack the metabolizing enzyme for codeine. Opioid naive patients should not be denied opioids as addiction is unlikely in acute pain. Nausea is a well documented side effect of morphine.

Medicines for long-term obesity management

Summary

Obesity is always genetic or epigenetic in origin in an obesogenic environment. Dietary therapy is required for weight loss.

Drugs to suppress hunger and increase satiety may assist while losing weight and are essential for most patients in the weight maintenance period. A combination of drugs may be needed.

A personalised approach must be used when selecting the appropriate weight loss drug for the patient. This considers possible contraindications, the method of administration and adverse effects, and includes discussing the cost of the treatment. Several drugs do not have an approved indication in Australia for weight loss.

Keywords : anti-obesity drugs, bupropion naltrexone, hunger, liraglutide, orlistat, phentermine, semaglutide, topiramate, weight loss

(Aust Prescr 2022;45:38–40)

Introduction

People with a body mass index above 30 kg/m2 have obesity. There is strong evidence that obesity has a predominantly genetic1
or epigenetic2 basis. All other proposed causes of obesity, such as our modern lifestyle, gut bacteria and sleep deprivation, can modify weight but, on their own, cannot cause obesity. If a genetically thin person is put in an obesogenic environment, they will produce leptin which suppresses hunger. Although they will gain weight, they may not develop obesity.

Forced overfeeding studies from America have shown that, despite a group of individuals being overfed by the same amount, there is a range of weight gain. Those not gaining weight spontaneously increased their daily energy expenditure by around 2000 kilojoules.3,4 The genetic basis of obesity explains why the body defends weight so vigorously. Following even modest weight loss, there are long-lasting hormonal changes that lead to increased hunger and a reduction in energy expenditure.5 This is why it may be helpful to consider using drugs to suppress hunger to assist with weight loss, depending on the diet being used to manage obesity. More importantly, these drugs are almost essential to help with maintaining the weight loss

Drugs used in long-term management

There are several drugs for weight loss available in Australia (see Table),6 however not all of them have an approved indication for obesity.

Phentermine

Phentermine is a sympathomimetic amine that acts on the brain to inhibit hunger.

Orlistat

Orlistat is an intestinal lipase inhibitor that slows fat digestion. It does not inhibit hunger, so it does not have a role in maintaining weight loss.

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist with a hunger-suppressing action. It requires a daily injection with a starting dose of 0.6 mg. Liraglutide can cause nausea which settles after continued use. The dose can be slowly increased up to 3 mg daily, if required.

Semaglutide

Semaglutide 1 mg is approved in Australia for the treatment of type 2 diabetes. It is given as a weekly subcutaneous injection. Although GLP-1 agonists lower glucose in patients with diabetes, they do not cause hypoglycaemia in individuals who do not have diabetes. This is because GLP-1 requires elevated glucose concentrations to stimulate insulin secretion.
Low doses work very well in a subset of the population, but higher doses are needed by some. For these patients a 2.4 mg dose of semaglutide has been approved by the US Food and Drugs Administration (FDA) and is under consideration by the European authorities for the treatment of obesity. Compared to switching to placebo after 20 weeks, continued treatment with semaglutide can sustain weight loss.7

Bupropion with naltrexone

The combination of bupropion and naltrexone works by increasing activity in the melanocortin system of the hypothalamus. The starting dose is one tablet (bupropion 90 mg/naltrexone 8 mg) daily, gradually increasing to two tablets twice daily

Table **Drugs used in the maintenance of weight loss**

Drug	Doses available	Mode of action	Adverse effects	Contraindications	Efficacy (placebo subtracted losses)	Cost*
Phentermine	15, 30, 40 mg once daily	Sympathomimetic amine	Dry mouth Difficulty with sleeping Increased heart rate and blood pressure	Coronary artery disease Cardiac arrhythmias Use of antidepressant drug	6.4% weight loss	$145/month at highest dose
Orlistat	120 mg three times a day with meals	Intestinal lipase inhibitor	Steatorrhea	Pregnancy or breast feeding	4.1% weight loss	$92/month over-the-counter
Liraglutide 3 mg	0.6–3 mg once daily injection	Slows gastric emptying Suppresses hunger	Nausea Diarrhoea Constipation	History of pancreatitis	7.0% weight loss	$387/month at highest dose
Semaglutide	0.25–1 mg weekly injection	Slows gastric emptying Suppresses hunger	Nausea Diarrhoea Constipation	History of pancreatitis	8.6% weight loss	$132/month for 1 mg for patients without diabetes
Bupropion 90 mg/ naltrexone 8 mg	1–4 tablets daily	Increases melanocortin system activity	Nausea Constipation	Use of opioid analgesia Use of phentermine	6.3% weight loss	$242/month at highest dose
Topiramate	25–100 mg daily	Unknown	Paraesthesia Confusion Fetal abnormalities (cleft lip)	Glaucoma History of renal stones Pregnancy	7% weight loss	$22/month

* Costs in 2021

Topiramate

Topiramate is an antiepileptic drug. It has not been approved by the Therapeutic Goods Administration for the treatment of obesity in Australia because no one has applied to register it for treating obesity. However, topiramate in combination with phentermine was approved for the treatment of obesity by the FDA in 2012. Topiramate has frequent adverse effects that occur at higher doses. These include glaucoma, renal stones, paraesthesia and confusion. In addition, it has teratogenic effects on the developing embryo (cleft lip). The starting dose should be low (12.5–25 mg daily) for obesity management and the maximum dose should be 100 mg daily in two divided doses of 50 mg.

Considerations in drug selection

Drug therapy is part of the management of obesity. Clinical trials include diet and lifestyle interventions so patients still need to make lifestyle changes to benefit from drug treatment. When to start drug treatment depends on the diet being used for the management of obesity. For example, drugs may not be needed in ketogenic diets because ketones suppress hunger. The selection of the first drug to try is informed by the presence of any contraindications. A history of epilepsy excludes bupropion/naltrexone, pancreatitis excludes liraglutide and semaglutide, cardiac arrhythmia excludes phentermine, and glaucoma, renal stone disease and planning a pregnancy would exclude topiramate. The second consideration is cost and there is also a need to consider which drug would be the safest to use long term.

Efficacy and safety

A dose that works well with no adverse effects for one individual could cause very severe and intolerable adverse effects in another. All prescribers should warn their patients about this, then, by mutual agreement, start one drug and be prepared to change to another if the first drug is not tolerated or is ineffective. Patients should be routinely monitored for adverse effects and the response to treatment.

Combination regimens

The body uses eight hormones to suppress hunger after a meal – cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide 1 (GLP-1),

oxyntomodulin, uroguanilin, pancreatic polypetide, amylin and insulin. It therefore makes sense that several drugs may be needed in combination to control hunger. If each medicine is used at a low dose, some of the adverse effects may be avoided. However, there is currently no evidence to support this approach.

Phentermine has been combined with topiramate and is available as a single capsule in the USA. In Australia, the two drugs can be prescribed separately.8 Liraglutide or semaglutide could be combined with phentermine and topiramate or the bupropion/ naltrexone combination. Phentermine should not be combined with bupropion/naltrexone. This is because bupropion has antidepressant effects and may increase cerebral serotonin. If that serotonin enters the blood stream, it normally would cause no harm, due to the avid uptake of serotonin by red blood cells. However, phentermine inhibits red cell uptake of serotonin so combining it with bupropion may increase circulating serotonin, which has been shown to cause heart valve fibrosis.

Treatment cost

Obesity rates are high in areas of low socioeconomic status. It is therefore important to consider the cost of the treatment when selecting a drug, a combination of drugs and the doses to be used. There is no subsidy for drugs that are approved for weight loss in Australia.

Duration of therapy

The hormone changes leading to increased hunger are very long lasting (at least six years, so probably life-long).5 This should be taken into account when considering which drug should be chosen, in addition to dietary therapy, for the maintenance phase of weight loss.

Conclusion

Weight loss drugs are one part of the ongoing management of obesity. They are useful during the weight loss phase, but are essential in the maintenance phase. Patients need to be informed about the cost of these drugs, in addition to discussing efficacy and safety.

Conflicts of interest: Joseph Proietto has been on the medical advisory boards for liraglutide, semaglutide 2.4 mg and bupropion/naltrexone. He has been involved in educational sessions for obesity management for both Novo Nordisk (liraglutide, semaglutide) and iNova (phentermine and bupropion/ naltrexone) for which he has received honoraria.

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