FACULTY OF
PAIN MEDICINE
of the Royal College of Anaesthetists

NEW EXAMPLE EXAM QUESTIONS

The FFPMRCA Court of Examiners has released these additional example questions from the FFPMRCA Examination question bank.

1 Multiple True False (MTF) questions
2 Single Best Answer (SBA) questions
3 Extended Matching Question (EMQ)
4 Structured Oral Examination (SOE) – Clinical questions
5 Structured Oral Examination (SOE) – Science question

Multiple True False (MTF) questions

1 Post-herpetic neuralgia is:

A a consequence of neurological damage caused by the Herpes Simplex virus (FALSE)
B more common in the elderly patient (TRUE)
C characterised by 'lightning' pain (TRUE)
D unresponsive to treatment with tricyclic antidepressants (FALSE)
E prevented by treating the acute phase with acyclovir (FALSE)

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2 The Brief Pain Inventory (BPI) questionnaire:

A was originally designed to assess pain in cancer (TRUE)
B cannot be self-administered (FALSE)
C uses word scores to assess the quality of pain (FALSE)
D assesses pain over the last month (FALSE)
E assesses the interference from pain on work (TRUE)

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3 Gabapentin:

A has a lower bioavailability than pregabalin (TRUE)
B acts primarily on GABA-A receptors (FALSE)
C causes seizures at high doses (FALSE)
D reaches its maximum plasma concentration 30 minutes after oral dosing (FALSE)
E is absorbed actively from the gut via a saturatable transport system (TRUE)

4 The coeliac plexus is :

A directly anterior to the crura of the diaphragm (TRUE)
B directly anterior to the inferior vena cava (FALSE)
C directly anterior to the aorta (TRUE)
D at the level of the L3 vertebra (FALSE)
E directly posterior to the pancreas (TRUE)

5 The descending pain inhibitory system includes:

A periaqueductal grey matter (TRUE)
B gamma efferent system (FALSE)
C locus coeruleus (TRUE)
D nucleus tractus solitaries (FALSE)
E nucleus raphe magnus (TRUE)

6 Glutamate:

A is an excitatory peptide neurotransmitter (FALSE)
B reuptake is modulated by glial cells (TRUE)
C binds to AMPA, kainate and NMDA receptors (TRUE)
D binds to G-protein coupled receptors resulting in sustained depolarisation (TRUE)
E is metabolised in the synaptic cleft (FALSE)

Single Best Answer (SBA) questions

1 A 57 year old man has complained of a shooting pain over his right cheek for 6 months. This can happen several times a day. The pain is worse in cold weather and can wake him at night. He is pain free between attacks. There are no abnormal findings on examination.

The most appropriate investigation is:

A CT scan of the head
B MRI angiography of the head
C orthopantogram (OPG) X-ray
D skull X-ray to include the zygoma
E upper cervical spine X-ray

Correct Response: B

Reasoning and Comments: This is trigeminal neuralgia.

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8 The highest dose of ionising radiation to the patient occurs during:

A bone density scan
B chest X-ray
C CT head
D CT spine
E isotope bone scan

Correct Response: D

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9 A 28 year old man comes to your pain clinic. He has had severe headaches for the last six months. The headaches are precipitated by drinking lager with his friends. He had similar headaches a few years ago but these got better.

The most likely diagnosis is:

A cerebral metastasis
B chronic daily headache
C cluster headache
D migraine
E tension-type headache

Correct Response: C

Extended Matching Question (EMQ)

Options:

A cerebral secondary malignancy
B cluster headache
C chronic daily headache
D migraine
E occipital headache
F secondary headache
G tension type headache
H trigeminal neuralgia

For each of the scenarios below, choose the item that provides the most appropriate answer from the above options. Each option may be used once, more than once or not at all.

1 A 20 year old student complains of generalised pain in the back of her head and neck that feels like a 'tight band'. Her headaches normally come on during the day, and get worse as the day goes on. **(Answer: G)**

2 This headache is commonly associated with an aura. **(Answer: D)**

3 This headache is commonly unilateral. **(Answer: D)**

4 This headache causes attacks that occur over several weeks or months and then remit for several months or years. **(Answer: B)**

5 This headache is the most common primary headache . **(Answer: G)**

Structured Oral Examination (SOE) Clinical questions

In the structured oral exam the examiner is instructed to ask the questions written in bold. Examiners are given examples of the topics that may be covered in the answer.

SOE LONG CASE: CENTRAL POST STROKE PAIN (CPSP)

A) Explore knowledge of central post stroke pain (CPSP) and demonstrate understanding of the psychosocial issues of CNMP

Candidate information:
A 75-year old man complains of pain in left arm and leg which started 1 month after a CVA about 2 years ago. He has mild COPD and controlled hypertension. He also complains of nocturia and is under investigation by the urologists. He has longstanding frequent headaches. His GP prescribed Gabapentin 100mg BD and Morphine Sulphate Controlled Release 10mg BD.

He is also taking:

- BendroflumethIazide
- Ramipril
- Salbutamol
- Aspirin
- Simvastatin
- Oxybutynin
- Lactulose

Findings on examination:

- Limited movement of the neck especially rotation.
- Mild residual weakness of the left upper limb > lower limb (dominant side)
- Mild sensory loss of the left arm (pinprick and temp)
- Allodynia over the left side of his body
- Reflexes- no abnormality
- His wife reports he has withdrawn from social interactions, his sleep is disturbed andhe has lost interest in his usual hobbies.

Supporting information:
Na 136, K 4.1, Urea 12.1, Creatinine 195. His GFR is 30.

What is the most likely diagnosis?
Central Post Stroke Pain (CPSP)

Are there possible alternative causes for his pain?
Unlikely since started post CVA and involves arm and leg –possible, if mainly arm pain then he could have OA neck or cervical disc prolapse.

Do the other ongoing problems contribute to the pain?
Discussion of pain and depression causing sleep problems and inability to manage the pain.

What do you know about CPSP?
Pain from a primary lesion or dysfunction of the central nervous system after stroke. Pain can be spontaneous or evoked and continuous or paroxysmal. Described as burning, pricking, shooting,

squeezing and throbbing. Allodynia and hyperalgesia associated with it and probably essential parts of the syndrome.

Can occur with ischaemic and haemorrhagic lesions at any level. Anywhere in spinothalamic pathway and its cortical projection. (Thalamic pain described after thalamic stroke in 1906). Probable that half of those with CPSP have lesions involving thalamus.

Pinprick, temperature and touch are impaired in 2/3 of CPSP cases. Distribution of pain in terms of frequency are arm, leg, trunk and face. Most common is hemi-body. Problems are usually contralateral to the side of the cerebral event.

Incidence 8%- 35% of all CVA. (Variation in inclusion criteria). 25% patients after CVA have somatosensory deficits. 85% of strokes are due to infarct so more CPSP seen after infarct.

When does it normally present?
Most in first month (60%) but can occur up to three years.

What is the likely pathophysiology?
Not well understood but central disinhibition, imbalance of stimuli and central sensitisation suggested. 'Wind up' and denervation hypersensitivity. Discriminative sensory deficit in CPSP results in disinhibition which results in spontaneous pain and allodynia. Central sensitization. Importance of sodium channels in central pain.

B) Pharmacological treatment

Would you expect to see any benefit from the dose of gabapentin prescribed?
Discussion of starting low and needing to increase, also discussion of dose modification in renal failure.

Other Rx?
Discussion pregabalin e.g. tolerance and cost issues.

Role of TCA?
Amitriptyline effective but may be contraindicated for this case. (50-70% will benefit)

Role of sodium channel blockade?
Lamotrigine moderately effective in CPSP. Regarded as second line treatment after TCA.
Little evidence for carbamezepine or phenytoin.

Role of NMDA antagonists?
Use of oral ketamine, possible as short term measure.

Role of opioids?
Morphine ineffective. Limited evidence for tramadol.

Is there a role for sympathetic blockade?
TENS-useful in patients who have not lost touch and vibration in painful area.

Is there a role for intrathecal drugs?
Limited evidence of value. Baclofen may be useful for spasticity when quality of life is affected

C) Need for multidisciplinary assessment treatment of the psychosocial issues
How many patients have fatigue and mood changes?

- 50% disturbed sleep and fatigue
- 87% mood changes

What questionnaires are you aware of that might help with the diagnosis of depression?

- HAD (Hospital Anxiety and Depression score)
    - 14-item scale – 7 depression, 7 anxiety.
    - Each item scored 0-3. Maximum score 21 for each. Likert scale. Validated. Cut off is 8/21.
- BDI (Beck Depression Inventory)
    - 21-question self-report scale. Severity and depth of depression symptoms over the previous week.
    - 0-3 for each question. Score over 17 indicates mild depression, over 40 severe depression. Not a diagnostic tool. Developed in mental health care setting. Used to evaluate therapy.
- Centre of Epidemiology study of Depression Index (CESDI)
- PSQ 9
- Zung
- Hamilton

Need for psychological intervention?

- Essential part of care as depression and other psychological sequelae are common.
- Psychosocial assessment to evaluate the perception of pain and disability and potential barriers to treatment. Influence of mood on pain. Anger/depression/distress.
- Cognitive factors – beliefs and attributions, coping strategies.
- Adjustment – familial, social.
- Possible options for treatment e.g. CBT, cognitive restructuring, relaxation techniques, mindfulness
- Imagery

What role do you see for acupuncture in neuropathic pain states?
Limited but sometimes useful.

Non- pharmacological treatment?
Motor cortex stimulation, deep brain stimulation and transcranial magnetic stimulation have been tried. Need for careful selection / in drug resistant only.

SOE SHORT CASE: EPIDURAL STEROIDS

What are the mechanisms of action of epidural steroids?

- Steroids primarily exert their inhibitory function via the lipoxygenase pathway to reduce theformation of leukotrienes.
- Cells exposed to glucocorticoids synthesize and release a phospholipase A2-inhibitoryglycoprotein, lipomodulin. The inhibitory action of lipomodulin reduces the formation ofarachidonic acid.
- Glucocorticoids stabilise leucocyte lysosomal membranes and prevent the release of destructive acid hydrolases from leukocytes

- Inhibition of macrophage accumulation in inflamed areas
- Reduce fibroblast proliferation, collagen deposition, and scar tissue formation.
- Suppress the production of inflammatory lymphokines and monokines including IL-1 and TNF

What are the systemic and local side effects of steroids?

- Endocrine- adrenal suppression, hyperglycaemia, hypokalaemia, amenorrhoea, menstrual disturbances, growth retardation
- Cardiovascular- hypertension, fluid retention, CHF, DVT
- Musculoskeletal- osteopenia, osteoporosis, avascular necrosis of bone, pathological fracture, muscle wasting and atrophy, muscle and joint pain
- Psychological- mood swings, insomnia, psychosis, anxiety, euphoria, depression
- Gastrointestinal- dyspepsia, GI bleed, diarrhoea, constipation
- Ocular- retinal haemorrhage, increased intraocular pressure, exopthalmos, glaucoma
- Dermatological- facial flushing, impaired wound healing, hirsutism, petechiae, ecchymosis, dermatitis, hyperpigmentation, cutaneous atrophy, hypopigmentation
- CNS - headache, vertigo, insomnia, restlessness, increased motor activity, ischaemic
- PNS - neuropathy

SOE SHORT CASE: ACUTE PAIN MANAGEMENT OF SICKLE CELL DISEASE

Introduction:
Sickle cell disease is the name given to a group of lifelong inherited conditions of haemoglobin formation. Red blood cells in people with sickle disease behave differently under a variety of conditions including dehydration, low oxygen levels and elevated temperature. Patients with sickle cell anaemia may suffer from

- Anaemia and sequelae
- Pain – acute, chronic and acute-on chronic
- Ischaemic organ damage / infections and comorbid conditions.

Acutely painful sickle episodes (painful crises) are characterised by the effects of sickle cell vaso-occlusion - micro +/- macro vascular which cause ischaemia, tissue damage and pain. Most crises last 5-7 days however the severity, frequency and duration can vary.

Scenario read to the candidate:
"A 18 year old female of Afro-Caribbean descent has attended the Accident and Emergency Department with hip pain from a sickle cell crisis. The advice of the pain team is sought by A+E staff to guide analgesia".

What information do you want to find when taking a clinical history from this patient ?

- Pain history - locations of pain, current and previous analgesics / history of pain interventions and how helpful these were.
- Assessment of possible causes of the sickle cell crisis – hypoxia, infection, dehydration, bleeding, alcohol and drug misuse and pregnancy. NB Often there is no predisposing cause.
- Assessment of associated conditions secondary to end organ damage – May be history of anaemia, stroke, renal impairment, pulmonary hypertension. Possible history of splenectomy (susceptibility to encapsulated bacteria – may be on long term prophylactic antibiotics)

What would you look for on physical examination of this patient?

- Airway / Breathing - shortness of breath (Secondary to Infection or 'Acute Chest Syndrome' characterised by SOB, fever and chest pain - may be hard to differentiate from chest infection).
- Circulation - Hypovolaemia may be manifested by tachycardia, hypotension, venous collapse (Note: splenic sequestration crisis - acute painful enlargement of the spleen, an emergency that may lead to circulatory collapse).
- Disability - Look for clinical signs of condition and associated comorbidities. Hip pain may be from avascular necrosis of the femoral head from vaso-occlusion or from osteomyelitis of the femur.

What Observations and Investigations would help you assess this patient?

- Vital signs and non-invasive SpO2 Blood Tests:
    - (I) blood gases
    - (II) FBC, in particular to quantify the extent of the anaemia and white cell count. Reticulocyte count, this reflects red cell production. Infection (especially by parvovirus) may reduce red cell production and precipitate a crisis (aplastic crisis).
    - (III) HbS %
    - (IV) U+Es
- IMAGING - X-Rays hip and femur / MRI hip and femur

Discuss acute pain management strategies for this patient?

(a) Analgesia

- Optimisation of analgesics stepwise from combined simple painkillers, through to strong opioids however renal impairment may contraindicate NSAIDS. Oral route preferred if possible however inpatient admission and intravenous opioids often needed (e.g. PCA). May be opioid tolerant already and PCA may need to be modified. Medication for neuropathic pain may be considered if indicated including ketamine acutely. Avoid Pethidine.
- Possible role for regional anaesthetic technique (various options including psoas compartment
  block), Trial of TENS.

(b) Condition – Specific

- Correction of any dehydration and hypoxia and dehydration.
- Aggressive treatment of infection if present.
- Interdisciplinary Care – Patients with acute sickle crises should by managed by acute medicine haematology specialists to treat underlying medical conditions and for further management such as blood transfusion to correct anaemia and its sequelae plus reduce the HbS %, also agents such as hydoxyurea (promotes fetal Hb production in place of HbS) may be indicated. Orthopaedic involvement for the treatment of AVN / osteomyelitis often from Salmonella and Staph. Aureus.

Structured Oral Examination (SOE) Science questions

In the structured oral exam the examiner is instructed to ask the questions written in bold. Examiners are given examples of the topics that may be covered in the answer.

NEUROPATHIC PAIN – DIAGNOSIS AND SCREENING TOOLS

Scientific principles:
Pain assessment in a subsection of the chronic pain population

Clinical application of Scientific Principles:
Neuropathic pain assessment

Question:

What is the definition of neuropathic pain?
IASP NeuP SIG 2007 : ''pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system".

How does this differ from the previous 1994 definition?
1) disease instead of dysfunction to exclude vague terms, 2) somatosensory instead of nervous system to exclude pure motor nerve pathology, which is not NeuP

Can you categorise NeuP into Possible, Probable & Definite?

- Possible - history of pain that fits characteristics and neuro-anatomical distribution
- Probable - requires the above plus either the demonstration of a neural deficit or gain (sensory, motor, autonomic) or diagnostic tests which document a specific nerve disease process or nerve lesion.
- Definite - requires all 3 of the above features.

What Special investigations might be done to confirm NeuP?

- Function - QST (Quantitative Sensory Testing)
- Pathology - blood (B12/folate, diabetic, alcoholic induced etc), CT, MRI, NCS/EMG, skin/punch biopsy.

What assessment tools are you aware of for NeuP?
Non specialised "generic" tools to measure multidimensional pain presentation. However SF Magill Pain Questionnaire relatively insensitive as discriminative tool for neuropathic pain.

Specific neuropathic pain assessment tools do not supplant clinical evaluation, can suggest /support the diagnosis. Most useful for non-specialists. All based on neuropathic descriptors and two of them (LANSS and DN4) also on simple examination findings. Validity issues due to "questionable" gold standard (demonstration of lesion as per neuropathic pain definition).

LANSS- Leeds Assessment of Neuropathic Symptoms and Signs. British. Physician administered. 7 weighted items, dichotomous: 5 sensory items, 2 clinical examination findings. Available as (self report) S- LANSS. Summed total 24, threshold 12 (>12 "neuropathic mechanisms are likely to be contributory"). Validated for NeuP in Cancer (multiple studies). Sensitivity 80%, specificity >90% (Similar to DN4).

DN4 – Dolor Neuropathique en 4 questions. French. Uses 7 interview questions and 3 physical tests

PainDetect- German. Self report. 9 items- 7 sensory, 2 measuring spatial/ temporal characteristics. Includes a drawing. Sensitivity 85%, specificity 80%. Validated for NeuP in back pain

NPQ - Neuropathic Pain Questionnaire. 10 sensory items (history and examination findings), 2 affect related.
66% sensitivity, 74% specificity. "Short form" of 3 sensory items similarly discriminative.

- StEP (Standardized Evaluation of Pain) combines six interview questions and ten physical tests for distinguishing neuropathic from nociceptive pain in low back pain. 90% sensitivity & specificity

NPS- Neuropathic Pain Scale- first specific neuropathic pain questionnaire. 11 point scales for pain intensity,

quality, temporal characteristics etc. Validated for response to treatment, NOT for diagnosis.

Filler - Epidemiology. How common is NeuP?
Neuropathic pain commonly reported to be around 2-4% of general population
Prevalence of POPNO "pain of predominantly neuropathic origin" 8% in UK – based on S-LANSS.
Prevalence data- possibly inaccurate related to diagnostic difficulty
27% pain clinic attendees have neuropathic pain- higher proportion in pain clinics compared with population prevalence- may reflect higher pain intensity/refractoriness to treatment/ associated disability.
Highest proportion most likely post surgery/accident related trauma.
Diabetic (25% DM develop NeuP), MS, post stroke pain (8% develop NeuP), PHN, TN Approx 25% peripheral neuropathies no cause found.

INTERVERTEBRAL DISCS AND DISC DISRUPTION

Scientific principles:
Structural lesions and pathology

Clinical application of Scientific Principles:
Diagnosis & treatment options of disc disease. Candidate must have good understanding of the anatomy and pathology of intervertebral discs.

Question:

Describe the anatomy of the intervertebral discs (IDs):

Structure?

- Thick outer ring of fibrous cartilage (annulus fibrosus), inner gelatinous nucleus pulposus, sandwiched by cartilage endplates
- Nucleus contains collagen fibres, organized randomly, and elastin fibres, arranged radially.
- Annulus is a series of 15-25 concentric lamellae, the collagen fibres lie parallel within each lamella.

Blood supply?

- Healthy disc has few blood vessels supplying it, most of the vascular supply terminates at the adjacent longitudinal ligaments.

Nerve supply?

- Ggrey rami communicantes, from the lumbar sympathetic trunks, join the ventral rami of the lumbar spinal nerves to form a mixed nerve, the ***sinuvertebral nerve***, which then supplies the posterior and posterolateral annulus fibrosus, and the posterior longitudinal ligament.

Describe intervertebral disc disruption (IDD) and its causes:

- IDD and disc herniations are common causes of low back and/or lower extremity pain.
- In chronically damaged IDs, leak nuclear material from annular tears - promotes inflammatory process.
- Mediators include matrix metalloproteinases (MMP), phospholipase A2 (PLA2), cyclooxygenase (COX), prostaglandins, nitric oxide (NO), cytokines, and interleukins.
- Infiltration of macrophages and other inflammatory cells may promote neovascularization in outer regions of the annulus.
- Central sensitization.
- Prolapsed lumbar discs account for less than 5% of all low-back problems, but are the most common cause of nerve root pain. Most lumbar disc prolapses resolve naturally

How can Disc degeneration be classified?

- Grade 0: Normal non-leaking nucleus.
- Grade 1/2/3: Annular tearing confined to inner 1/3,2/3 or 3/3 of the annulus fibrosus.
- In grade 3 during discography, contrast material leaks out of the back of the disc into the epidural space.
- The presence of a disc bulge and/or disc herniation is also included in this category.

What are the Risk factors/causes?

- Genetic inheritance accounts for 70%
- *Ageing changes:* proteoglycans bind water, when they fragment lead to dehydration and decompression of nucleus. Mechanical stress concentrated on annulus. Collagen crosslinks of annulus form, stiffer, less able to absorb energy with loading, less able to remodel i.e. more vulnerable to injury.
- *Repetitive loading*, microscopic damage
- *Impaired nutrition,* already avascular ie at risk; assoc. with smoking
- **Supplementary** if earlier covered: Interventional treatments possible based on above pathologies but vital to demonstrate appreciation of limited and controversial evidence for:
    - Provocative discography – for diagnosis
    - Discectomy – removal of damaged portion of disc
    - IDET/ nucleoplasty/ bipolar annuloplasty etc
    - Intervertebral fusion

ANTIDEPRESSANTS

Scientific principles:
Putative mechanisms of action of antidepressants

Clinical application of Scientific Principles:
Rationale for antidepressant prescriptions for pain. Knowledge of side effects and serotoninergic

syndrome**.**

Question:

What classes of antidepressants do you know, and give some examples?

- Tricyclic antidepressants (TCA): e.g. amitriptyline, nortriptyline, imipramine
- Serotonin-Noradrenergic Re-uptake inhibitors: SNRI: e.g. duloxetine, venlafaxine
- Selective-Serotonin Reuptake Inhibitors (SSRI): e.g. Fluoxetine, paroxetine, citalopram
- Monoamine Oxidase Inhibitors: e.g. Phenelzine, Tranylcypromine
- NaSSAs : (also sometimes called Tetracyclics) Noradrenergic and specific serotonergic antidepressants (NaSSAs) are a class of antidepressants. They act by antagonising various adrenergic and serotonin receptors, typically α1-adrenergic and α2-adrenergic, and 5-HT2A, 5-HT2C, and 5-HT3, respectively. For example: Mirtazapine

Why may antidepressants act as analgesics for people in pain?

- Mode of action:thought to act via several mechanisms which include increased supraspinal availability of noradrenaline (thought to enhance descending inhibitory bulbospinal control), activation of endogenous mu opioid and delta-opioid receptors, sodium channel blockade, and NMDA receptor inhibition, plus activation of potassium channels, and calcium uptake inhibition. Tricyclics may also have a peripheral action via P2X receptors.
- Tricyclics can also cause sedation and may help if patient not sleeping at night.

Are tricyclics more effective than other antidepressants for pain?

- NNT for tricyclic antidepressants for neuropathic pain is about 3.1.
- SNRIs (Venlafaxine, Duloxetine) are used for neuropathic pain but have an NNT=5 approx. SSRIs (Fluoxetine) do not appear to be good analgesics NNT=7
- Tricyclics have more diverse modes of action-hence more effective, but also more side effects Duloxetine effective in DPN, fibromyalgia, Generalised Anxiety Disorder, stress incontinence.

What are the adverse effects of tricyclics?

- Postural hypotension, somnolence, weight gain, constipation. Anticholinergic effects, drug mouth, caution in glaucoma, hesitancy, caution in prostatic hypertrophy. Increased risk of arrhythmias. Caution in epilepsy Contraindicated after MI for one year.
- NNH for TCAs: 15.9 (11-26) similar to SNRIs: 13.1 (9.6-21). NNH for SSRI > 25 -better tolerated, less effective

Can Tricylics be used in children? What are the reasons for using Tricyclics in children?

- Yes. Starting dose amitriptyline: 200-500 micrograms/kg, then increased as necessary. Used for nocturnal eneuresis and neuropathic pain. No evidence for efficacy in depression. Caution in heart disease, esp. arrhythmias.

Tell me about serotoninergic syndrome? What drug combinations can cause this?

- Serotonin syndrome (SS) is caused by excess serotonin (5-hydroxytryptamine; 5-HT) availability in the CNS at the 5-HT1A-receptor. Suspect it in the setting of the recent addition of a serotonergic agent.
- Constellation of symptoms. Hunter criteria are simpler and more sensitive than older Sternbach's Clonus, agitation, sweating, tremor, hyperreflexia +. If have hypertonicity or T > 38°C require hospital admission

Most common drug combinations causing the serotonin syndrome are:

- Monoamine oxidase inhibitors (MAOIs) and serotonin selective reuptake inhibitors (SSRIs), MAOIs and tricyclic antidepressants
- MAOIs and tryptophan MAOIs and pethidine.
- More recently, tramadol plus tricyclics, SNRI or SSRI antidepressants. Many patients are on this combination.

SS is generally associated with a favourable prognosis. The management of SS encompasses five basic principles. What are they?

- Provide necessary supportive care
- Discontinue all serotonergic agents
- Anticipate potential complications
- Consider administering anti-serotonergic agents (cyproheptadine), and
- Reassess the need for psychopharmacologic therapy before reinstituting drug therapy.
- Approximately 42% of patients in published case reports of SS required admission to an intensive care unit and 24% of patients required intubation and ventilatory support. Most patients show some improvement within the first 24 hours after symptom onset with supportive care alone.

PRE-EMPTIVE AND PREVENTATIVE ANALGESIA

Scientific principles:
Pre-emptive vs preventive analgesia

Clinical application of Scientific Principles:
Peri-operative/ acute pain management

Question:

What is meant by pre-emptive analgesia, How does it differ from preventive analgesia?

- Pre-emptive analgesia: Analgesia given **prior** to an injury or adequate **noxious stimulus**. It prevents the nociceptive barrage that leads to central sensitisation, thereby preventing or reducing ongoing pain.
- Prev**entive** analgesia: An analgesic is said to have a preventive effect if its administration leads to a reduction in pain or analgesic consumption that extends **beyond its expected duration of action** (usually arbitrarily set at 5.5half lives).
- The principal **difference** is that in pre-emptive analgesia the focus is on the ***timing*** of an intervention i.e. before or after an incision, whereas for preventive analgesia the focus is on the effect of the intervention on the expected ***duration*** of analgesia, regardless of when the administration takes place in relation to an injury.

Can you briefly describe the underlying physiology and theory/ theories?

- **Mechanisms.**
    - C-fibre mediated nociceptive barrage from the periphery at site of injury induces secondary changes leading to central sensitisation. Abolition of this initiating event should prevent secondary changes and thereby reduce ongoing pain.
    - Theory supported by in vitro and in vivo laboratory investigations.
    - However, nociceptive barrage continues throughout surgery, relative importance of initiating or subsequent inputs in producing sensitisation not clear.

- **Preventive analgesia** is a much broader concept acknowledging that multiple factors may be involved in the sensitisation process. Preventive effects may be clinically more relevant, a number of drug combinations have been shown to have preventive effect.
- If an analgesic is capable of reducing sensitisation then its effects would be expected to extend beyond its normal duration of action, this may or may not be related to timing of administration.

Has pre-emptive analgesia proven to be clinically useful, discuss the reasons for this? What about preventive analgesia?

- Clinical usefulness of pre-emptive analgesia disappointing. Research evidence weak and contradictory. Reasons: too simplistic theory, differences in clinical trial design, difficulties in completely blocking nociceptive inputs, use of many different outcomes.
- Preventive probably more useful; broader concept and better defined outcomes i.e. reduction in pain scores or analgesic consumption at a time point beyond expected duration of target drug(at least 5.5 half-lives).

Discuss NMDA receptor antagonists and preventive analgesia.

- Ketamine (0.1 to 0.5 mg/kg/hr infusion) reduces hyperalgesia/allodynia and opioid consumption after surgery. Effect lasts longer than expected duration. Useful for chronic/cancer pain patients or uncontrolled acute pain.

Describe how you would design clinical trials to investigate these two effects.

- Pre-emptive; active treatment vs placebo, before or after incision (after group might be intra or postop), discuss use of negative (placebo vs placebo) and positive (active vs active) controls.
- Preventive; might include above design(s) and co administration of 2 active treatments etc**.** Importance of clear outcome definition.