FACULTY OF PAIN MEDICINE
AUSTRALIAN AND NEW ZEALAND COLLEGE OF ANAESTHETISTS
ABN 82 055 042 852

EXAMINATION HELD ON 25th to 27th NOVEMBER 2009

at THE ROYAL NORTH SHORE HOSPITAL, SYDNEY

THIS REPORT IS PREPARED TO PROVIDE CANDIDATES AND SUPERVISORS OF TRAINING WITH INFORMATION ABOUT THIS EXAMINATION AND TO ASSIST WITH PREPARATION FOR FUTURE EXAMINATIONS. ANSWERS PROVIDED ARE NOT MODEL ANSWERS BUT GUIDES TO WHAT MIGHT BE COVERED.

SOME ANSWERS CONTAIN MORE INFORMATION THAN COULD BE COVERED IN THE FIFTEEN MINUTES, BUT HAVE BEEN INCLUDED AS A TEACHING AID. THE ANSWERS PROVIDED ARE CONSIDERED CURRENT, BUT MAY BE SUBJECT TO CHANGE IN THE FUTURE.

CANDIDATES SHOULD DISCUSS THE REPORT WITH THEIR TUTORS SO THAT THEY MAY PREPARE APPROPRIATELY FOR FUTURE EXAMINATIONS.

The Examination is an integral part of the Pain Medicine Training Program, leading to the award of Fellowship of the Faculty of Pain Medicine.

The Objectives of Training guide the range of content, which may be assessed.

The Examination consists of written and oral sections and covers the theory and practice of Pain Medicine.

In 2009, 24 candidates presented for the examination and 20 were successful.

EXAMINATION **PASS RATE 83.3%**

WRITTEN SECTION (See Appendix A for guides to question answers)

WRITTEN SECTION **PASS RATE 62.5%**

General information:
As always candidates need to:

- Plan their answer so that it flows to appear to have an organised approach.
- *Answer the question as set -- not the question you would prefer to answer.*
- Give succinct answers and not repeat yourselves.
- Use headings and dot points if asked to discuss the answers briefly.
- Discussion does require explanations & consideration of alternatives.
- Give definitions if asked to discuss some aspect (e.g. personality and personality disorders or breakthrough analgesia). Do not assume examiners know what you understand by a term.
- Apply more commonsense thinking when answering the questions.
- Start answer with “I would do…” if asked to “outline your approach”.

The following are the questions. The first five questions were compulsory.

QUESTION 1 COMPULSORY PASS RATE 83.3%

A patient 32yrs with chronic back pain is admitted to a rehabilitation unit for a functional restoration programme. He reports taking Controlled Release Oxycodone 200 milligrams, three times daily.

Discuss the potential benefits and difficulties involved in changing the patient to daily Methadone.

Candidates needed to:

- Read the question carefully
- Differentiate between use of methadone for pain management and for addiction
- Check conversion ratios carefully

QUESTION 2 COMPULSORY PASS RATE 62.5%

A 39 year old woman reports persistent pain in her left iliac fossa three months after the repeat caesarean delivery of her child. List the differential diagnoses. How would you attempt to prevent acute pain becoming chronic in this case?

- Many candidates did not answer the question.
- There are two parts: differential diagnosis and discussion of prevention of chronicity
- The question was asking for prevention of the development of chronic pain beginning at, all before the time of surgery not following the time of consultation.
- Many did not recognise that at three months, pain is already chronic.
- Few mentioned that the evidence for prevention of transition to chronic pain is poor.

QUESTION 3 COMPULSORY PASS RATE 33.3%
(broad spread of marks)

Nausea and vomiting can be common side effects of long-term treatment with opioid analgesics. Discuss the mechanisms by which opioids produce nausea and vomiting. What management options are available?

This question was poorly done with nearly 2/3 failing & half of those who passed achieving the minimum pass mark.
Problems:

- Failure to read the question.
- Failure to answer the question.
- Too many concentrated on treating the nausea and vomiting.
- Inadequate detail regarding the physiology of nausea and vomiting produced by opioids.
- Very few mentioned the vomiting centre -- only one drew a diagram.
- Drug management was not well handled: some candidates discussed propofol and long-term steroid.
- Most discussed opioid rotation.
- Non-drug management was well covered by some candidates.
- No-one discussed the avoidance of other emetogenic drugs or exclusion of other causes of nausea and vomiting.

QUESTION 4 COMPULSORY PASS RATE 75%

Describe the "indicators" (Clinical symptoms & signs) of central sensitisation and discuss potential mechanisms.

- Candidates were asked to define clinical features and discuss. -- There was little discussion of many lists and given there were no statements indicating degrees of controversy and little mention of evidence levels.
- The good answers began with a definition of sensitisation and mentioned pain; gave examples of known syndrome; then described what the patient describes (i.e. symptoms) and what one finds on physical examination (i.e. signs).
- They defined the terms commonly used and referred to sensory, motor and autonomic signs and then listed mechanisms AND discussed and offered evidence or described animal versus human evidence
- The bad answers just gave a list which didn't discriminate signs from symptoms and didn't give more than the sensory symptoms.
- The poor answers simply gave a list of neurotransmitter related theories.
- Very few people made any attempt to discuss.

QUESTION 5 COMPULSORY PASS RATE 70.8%

Discuss the psychosocial factors that have been demonstrated to influence outcomes of lumbar spine surgery.

QUESTION 6 NON COMPULSORY

Attempted by 11 candidates PASS RATE 81.8%

Discuss the pharmacogenomics in the management of pain.

Generally well answered question.

QUESTION 7 NON COMPULSORY

Attempted by 16 candidates PASS RATE 43.8%
(Bell curve mark distribution - top mark 8)

You are a member of an acute pain service. The surgeon is keen for a patient undergoing an open hemicolectomy to be part of their 'fast-track' program, with early discharge planned at 4 days.

Discuss your approach to pain management in this situation.

- This question asked for a pain management plan: many candidates did not appear to recognise the specific requirements for this compared with pain relief generally.
- Some outlined criteria for patient selection for fast track surgery which was not part of the question.

QUESTION 8 NON COMPULSORY

Attempted by 21 candidates PASS RATE 42.9%

What are the methods available to prevent the evolution to and severity of Post Herpetic Neuralgia?

- Candidates generally failed to answer question.
- They provided a list of treatments for PHN -- and not treatments to reduce incidence/severity of PHN.
- Few addressed the role of childhood and adult vaccination.
- Time was wasted on definitions and epidemiology.

QUESTION 9 NON COMPULSORY

Attempted by 6 candidates PASS RATE 83.3%

An East African refugee is referred to your outpatient pain clinic with persisting widespread pain. He reports a history of imprisonment and interrogation. How does this history influence your evaluation?

Generally a well answered question.

QUESTION 10 NON COMPUSORY

Attempted by 0 candidates PASS RATE N/A

Discuss the concept of "tertiary gain" in relation to persistent pain.

QUESTION 11 NON COMPULSORY

Attempted by 22 candidates PASS RATE 63.6%

Why should you advocate the development of an acute pain service at your hospital?

The pass rate for this section was disappointing since this question has appeared in a slightly different format in several past exams. Many candidates discussed advocating for better pain relief but the question required arguments for advocacy of an acute service.

QUESTION 12 NON COMPULSORY

Attempted by 23 candidates PASS RATE 65.2%

A 71 year old male patient presents with severe metastatic bone pain secondary to prostate cancer. Discuss the evolving pathophysiology of cancer related bone pain and the evidence for novel analgesic therapies.

One third of candidates performed badly.
While this is possibly not core knowledge, theories of the pathophysiology of metastatic cancer pain are prominent in the literature.
Candidates wasted valuable writing time rewriting the question
Candidates should:

- Answer the question asked, not what they think should have been asked.
- Have a structure to the answer, do not write lists or provide one word answers if discussion is requested.
- It is accepted that dot points should be used in answering -- particularly where a list or an outline is requested.
- Dot points help in discussion and should not be mistaken for a list without discussion which does require explanations & consideration of alternatives.

QUESTION 13 NON COMPULSORY

Attempted by 1 candidate PASS RATE 0%

You are asked to attend a hospital seminar on euthanasia to discuss the chronic pain aspects in a panel discussion. Outline your preparation for this discussion.

QUESTION 14 NON COMPULSORY

Attempted by 15 candidates PASS RATE 33.3%

You are referred a patient for a procedure to help control chronic pancreatitis related pain. Discuss your approach to this request and justify your position.

QUESTION 15 NON COMPULSORY

Attempted by 5 candidates PASS RATE 80%

Write brief notes on a recommended set of "core outcome measures" for clinical trials evaluating new analgesic agents for persistent non-cancer pain.

Generally well done but some candidates did not address reliability and validity measures.

General comments:

- Read question carefully
- Discuss rather than just give a list
- Some generic answering (e.g. Neurotransmitter theory)

LONG CASES PASS RATE 82.6%

General comments and observations:

Marks are given equally for History, Examination, and Presentation of findings in a logical manner, and a Management plan.

The candidates and the patients are both advised to ignore the examiners.
Aim is to establish rapport with the patient.

- Supervisors of Training are reminded they need to sign off that candidates have done *five observed long cases under exam conditions* prior to presenting to the examination.

- As the long case mirrors a first consultation within a pain clinic, we believe it should be retained.

- An outline of "How to take a Pain History" is available in the NHMRC booklet, Acute Pain Management: Scientific Evidence.

- Candidates all have access to the Pain Orientated Physical Examination (POPE) DVD.

- Candidates need to practice long cases under exam conditions as time management is essential.

- Start with open-ended questions, ensuring that history taking is patient centred.

- In the long case (and also at the communication station), when candidates ask closed questions, they become too focused too early.

- Listen to the patient. Patients give important clues, which at times are missed by the candidates.

- Attention to the psychosocial history was good in some cases.

- Candidates should ensure that they give appropriate time to examining the main area / systems affected by the pain, and consider examining this first.

- Candidates should spend a couple of minutes only on the examination on the systems NOT involved in the main area of symptoms.

- Demonstrate empathy and sensitivity. (Recall this interaction is being observed.)

- Remember pain may not be the major issue, but more disability or psychological dysfunction.

- Candidates need to assess pain, function, co morbidity and underlying disease.

- Presentation should be structured and the discussion objective.

- In presenting their conclusions candidates should consider:
    - An initial brief summary of the most pertinent data.
    - Their analysis of this, reflecting their judgement regarding the priorities and relevance of issues.
    - Considered in relation to predisposing, precipitating, perpetuating and aggravating factors.
    - Management in accordance with the above.

- An experienced candidate will present this information in less than seven minutes, even with a complex scenario, making use of the concepts outlined above, without needing to use the above terms.

- It is acceptable to indicate in your summary that there was particular information that you would have liked to obtain but did not. (Remember in real life we all may forget, and obtain the information at subsequent consultations.)

- Examiners need evidence that the candidate has the ability to be the leader of the Pain Team, and to manage the long case as if they were their own patient.

- Candidates are expected to finish their summary with a (biopsychosocial) diagnostic formulation and outline a management plan.

- Needs to be an emphasis on an **all round approach** to assessment, diagnosis, formulation, management and prognosis.

- Remember the patients who agree to be involved in the exam will be a reasonably select group. They will, as a rule, be "more than willing to please". Candidates should use this advantage, and follow up on any clues given.

- Candidates should expect questions on:
    - Mechanisms.
    - What to do if pain progresses.
    - What are the main pathophysioplogical issues?
    - What are the main patient related issues?
    - What are the main management issues?

- Candidates need to look beyond the current management and ask what else could be offered.

- Do not assume because the patient has been to a Pain Clinic all that is possible has been done. Also do not assume the treatment that has been done so far is "best practice".

- Be prepared to critically discuss the patients' current management and what you may do that is different from the plan patient has described.

***This year, long case patients were*:-**

- ***well chosen with interesting pain problems***
- ***good historians***

Ms MI: 67 -- Chronic Daily Headache/Migraine/Analgesic Overuse

Ms VR 64 -- Vulvodynia/Trigeminal Neuralgia/CSF Leak

Mr RR 68 -- Paraplegic -- chronic spinal pain, shoulder disruption, renal transplant

Ms MB 70 -- Trigeminal neuropathic pain following failed microvascular decompression /sever depressive disorder

Mr GA -- Spinal pain/cardiomyopathy/multiple comorbidities

Ms DC -- Multiple abdominal surgeries/injectable opioids

Mr SD -- Spinal pain

Ms JF -- Bowel dysmotility/Ehlers Danlos type III /opioid issues

Ms JG -- Post- mastectomy neuralgia/new breast malignancy

Overall, candidates performed reasonably well.
More care with timing of physical examination required.

STRUCTURED VIVA SECTION **PASS RATE (overall) 91.3%**

General information
The viva section consisted of three structured vivas and the investigation station.

Candidates need to be able to explain to the examiners, as they would to patients, what they mean by the terms they use.

Issue: candidates need to carefully read the question and accurately address what the instructions require.

- Candidates should expect questions on:
    - Nature of the lesion.
    - Anatomy.
    - Possible therapies for current pain.
    - Investigations to confirm your diagnosis.

The introductions to the structured vivas were as follows:

Acute Scenario **PASS RATE 65.2%**

Statement:
28-year-old naval seaman following a high-speed motorbike accident sustains a displaced fractures of cervical, thoracic and lumbar vertebrae with epidural haemorrhage but no cord or nerve root injury. He also has a significant crush injury to his right lower leg.

After three days it is decided that the leg is not viable and that he will require a right below-knee amputation (BKA)

Questions:
What would you suggest for perioperative pain management?

Key points:

The pass rate for this section was disappointing. Candidates generally fail to recognise that the patient had multiple injuries not just a leg injury: therefore, not all of the components of a standard 'drop-down' list of analgesic agents or techniques would be suitable in this particular patient. Some suggestions for management were potentially dangerous.

Chronic Scenario **PASS RATE 95.6%**

Statement:
A 16-year-old boy, the eldest son of a caring family, presents with recurrent severe right arm pain.
When 12 years old, he fell from a trampoline and suffered a mid-shaft fracture of his right forearm which was internally fixed by open reduction.
It was complicated by a compartment syndrome and intense post-operative pain.
After six weeks of immobilisation he was diagnosed with Complex Regional Pain Syndrome.

Questions:
1a: what factors might have predisposed this boy to a persistent pain problem?

Key points:

Generally well performed.

Cancer Scenario **PASS RATE 78.2%**

Statement:
The 54-year-old gentleman with metastatic melanoma to brain, cervical spine and chest wall. He is still receiving active treatment by his oncologist.
You are asked to see the patient regarding the persistent pain in one week after cervical fusion.

Questions:
What mechanisms might account of his pain?

Key points:

Generally well performed

Investigations Station **PASS RATE 78.2%**

Imaging, biochemical studies, etc - cases are taken from hospital files and on-line radiology images & standardised to a relatively straightforward case level (no tricks or esoteric cases). No normal results or images were shown.

General information

- Candidates need to attend regular X-ray meetings. (e.g. weekly)
- Candidates should use general knowledge.
- If there is an obvious diagnosis, mention it as soon as possible.

Specific examples:
Bone scans with disc disease
MRI with spondylolisthesis
Cervical scans with myelomalacia
Abnormal biochemical profile.

This year, most candidates had confidence in interpreting X-rays etc

Experienced candidates moved quickly through this section and did extremely well.
The section was generally well done.

SHORT CASES: **PASS RATE 82.6%**

Short Cases with Patients:

General information

- At each station, information was provided outside the station door.
- Candidates have 10 minutes and were directed to a specific area to examine or to impart information.
- This section is a test of physical examination techniques or communication skills.
- Candidates need exposure to Neurologists and Rehabilitation specialists as part of their training.

The Short Case section involved six patients - candidates are exposed to three.

Acute

- *A 51-year-old male presents following a fall off his bicycle. He has severe pain in the upper limbs associated with widespread neurological findings.*

  Please note that movement of the upper limbs causes significant pain. The patient is not allowed to move his neck.

- *A 69-year-old female presents with post-operative chest pain following thoracotomy four days ago.*

  PLEASE EXAMINE HER CHEST

Chronic

- *AB 52-year-old male -- presents with claudicant pain (exercise tolerance <20 metres) following aorto-duodenal fistula in December 2004.*

  LOWER LIMB EXAMINATION

- *KH 49-year-old male -- with ongoing pain in the right upper limb for 19 years following waterskiing accident.*

  UPPER LIMB EXAMINATION

Cancer

- *KB 66-year-old male -- presents with ongoing severe left chest pain following thoracotomy in 2006 for non-small cell lung cancer.*

  RESPIRATORY EXAMINATION

A few candidates had a systematic examination technique and there was variability in interpretation of signs and formulation of diagnosis.
Some candidates demonstrated a lack of skill on how to do this examination.

- *SB 40-year-old male -- presents with ongoing pain left upper limb over four years following diagnosis of Ewing's sarcoma in left supraclavicular fossa.*

  UPPER LIMB EXAMINATION

This year, some candidates failed to read instructions carefully or address the specific issues.

Communication Station **PASS RATE 91.3%**

COMMUNICATIONS VIVA

General information:

- This station involves an actor and is looking at communication skills. The candidate should not delve too much into the history. The history given should be all that is required.

- The aim of this station is to encourage a generalised discussion of why suggested options are preferable. Informed consent may be required.

- Details of the history, and the treatment plans are not necessary.

Instructions to the Candidate

You have been asked by the Director of your unit to assess Mr. Johnston, and to discuss further management with him. As this has been added on to your busy Outpatient Clinic, time for the interview is limited to 10 minutes.

(A copy of the following letter of referral will be on the desk in the interview room during your brief appointment with Mr. Johnston).

Dear Doctor,

Mr. Johnston has a 14 year history of uncomplicated back pain which continues despite extensive investigation and treatment.

Several surgeons have recommended against surgery and no further active interventions have been planned.

Despite a stable marriage, there is considerable domestic stress. His 7 year old son is frequently hospitalized for severe Congenital Heart Disease which may require transplantation.

He has been prescribed pethidine by his usual GP, since 2002. While there have been no complications, I am not comfortable providing a prescription and would appreciate your support.

Allergies: Morphine

Medication:

- *Pethidine 100mg twice daily*
- *Ibuprofen 1 bd*
- *Diazepam 5mg qid prn*
- *Esomeprazole 40mg daily*
- *Panadeine Forte 4 per day, prn*

Yours sincerely

Dr Veronica Noble
MB MS FRACGP

This station was generally well performed.

OVERALL EXAMINATION COMMENTS:

- Candidates may irritate painful areas in pain patients. This is recognised by examiners and allowance is made.
- Marks were also given for candidates recognising patients' sensitivities.
- Candidates need to know when it appropriate to probe and when not to, in both history and physical examination.
- Emphasise need for a thorough physical examination based on observations of long and short cases.

Leadership and team membership:
Part of the Pain Medicine Examination assesses the pain physician's involvement in a team, leadership issues and also the ability to critically evaluate the roles of other team members.
A number of candidates called for consultations with other team members in structured viva and long case answers -- the answer generally requires an assessment of *what is expected from other team members or consultants.*

The role of examination observers is extremely important:
External observers bring different perspectives and assist greatly in transparency and quality assurance. New examiners are able to critically evaluate the strengths and possible difficulties with each examination section. Drs Di Pacey, Owen Williamson and Wilbur Chan provided helpful observer's comments.

We are extremely grateful to Prof Michael Field *(FRACP)*, Associate Dean University of Sydney University School of Medicine for his observation of this examination and for advice for maintenance of standards and of transparency.
We continue to stress the importance of maintaining full transparency in the exam process and to provide clear guidelines of the level of rigour required of the candidates.

This year, the examiners were particularly mindful of pacing and timing at each exam station.

Special thanks must be given to Dr Paul Wrigley for his great efforts in efficiently organising the patients and the Exam Venue and to the staff of the RNSH Department of Pain Management and Research for their assistance with the examination rooms.

THE BARBARA WALKER PRIZE
The Barbara Walker prize is awarded to the leading candidate provided the total mark is above 70%.

This year the prize was not awarded.

Merit award
Candidates who performed with excellence and were in the top 10%.

A merit award was awarded to:

- Dr Kerry Thompson, Vic
- Dr Cliff Timmins, Qld
- Dr Max Sarma, Tas

RAY GARRICK	**MEREDITH CRAIGIE**
Chairman	**Deputy Chair**
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December 2009	

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APPENDIX A

QUESTION 1 ***COMPLUSORY***

A patient 32yrs with chronic back pain is admitted to a rehabilitation unit for a functional restoration programme. He reports taking Controlled Release Oxycodone 200 milligrams, three times daily.

Discuss the potential benefits and difficulties involved in changing the patient to daily Methadone.

Answer Guide

Benefits

- High oral bioavailability (70-90%)
- Convenient availability in liquid, tablet and parenteral formulations
- Includes alternative analgesia mechanism (NMDA antagonism)
- Twice daily doses for analgesia
- Relatively inexpensive
- Reduced "likeability"
- Provides safe opportunity to wean from opioid if opioid-unresponsive
- Clonidine cover (analgesic and reduce abstinence symptoms)
- Less likely to cause obesity and reduced sex hormones
- "Tried and true" in patients with addiction problems

Difficulties

- This case: 600mg/day is VERY high dose.
  More information is needed: RISK ASSESSMENT/Opioid Risk Tool (ORT):
  - Is he really taking that much? Consider diversion a high risk here.
    - Check last pharmacy dispensing/quantity; expect to bring own supply when admitted. Is amount remaining consistent with dispensing and reported use?
    - Have a staff member initially observe him taking "usual dose". Refusal should arouse concern. If taken, careful observation (beware: some will call bluff).
  - IF consumption seems as reported, but not pain controlled and/or functioning poorly, consider:
    - opioid unresponsive pain? ---> plan to wean from opioid
    - **OR**, opioid induced hyperalgesia (OIH)? Ditto
    - **OR** Methadone as better analgesic than oxycodone
      (not all opioids equal effects).
- Drug conversion formulae unreliable (may even be dangerous).
  up to 100 [3 : 1] Morphine to Methadone
  200 to 300 [5 : 1]
  600 to 800 [10:1] *as a guide.*
- Pharmacokinetics have marked individual variability
- Metabolised by cytochrome P450 enzymes (3A4,1A2, 2D6), therefore potential drug interactions eg Phenytoin, Carbamazepine, Ketaconazole, Fluoconazole, Clarithromycin, Rifampin. In addition, Topamax may increase Methadone half-life.
- Potential for high doses to prolong QTc interval (risk sudden cardiac death), particularly over 120 milligrams. Family history of sudden young unexplained deaths for congenital prolonged QTc? Does not capture all patients at risk.

- Careful observation to avoid cumulative toxicity. May take twelve days to reach steady state.
- Negative attitudes of patient, due to stigma, connotations.
- Drug diversion (trading) and compliance monitoring :
    - Urine Drug Testing
    - “Pill counts” (or check bottle liquid levels)
- General practitioner needs supportive education and ongoing confidence.
- About 30% of patients develop disorder of breathing during sleep (central sleep apnoea).

QUESTION 2 ***COMPLUSORY***

A 39 year old woman reports persistent pain in her left iliac fossa three months after the repeat caesarean delivery of her child. List the differential diagnoses.

How would you attempt to prevent acute pain becoming chronic in this case?

Differential Diagnoses

Intra abdominal pathology

Large Bowel Diseases
Diverticular Disease
Crohn's Disease
Ulcerative Colitis
Partial bowel obstruction
Irritable Bowel Syndrome

Pelvic pathology

Abdominal collection
Granulomatous peritonitis
Disorders of urinary/uterine/ovarian/tubal origin
Viscelar neuropathic disorders

Neural pathology

Spinal cord lesion
Intercostal neuropathy
Abdominal cutaneous nerve entrapment
Myofascial pain syndrome
Scar pain

Psychological pathology

Somatoform pain disorder
Delusional/hallucinatory pain
Hysterical/hypochondriasis
Depression

Answer

Persistent pain reported after three months following a caesarean section could be regarded as chronic pain by definition. Currently there is no good evidence that any specific interventions alter the progression of acute pain to chronic long term pain.

Even so specific interventions are known to reduce the severity of the pain experience and subsequent long term disability related to the pain. Reducing the severity and duration of the pain experience, should have some influence on the long term suffering of these patients.

After an initial evaluation of the pain process in terms of history and physical examination from a multidisciplinary team and possible consultations with other medical specialties, correctable causes for specific diagnoses should be excluded.

Once specific correctable pathology has been excluded or treated, as well as it can be, and pain remains as a substantial cause for disability and suffering, the pain process should be treated to improve function and reduce suffering.

The use of tricyclic or serotonin noradrenaline reuptake inhibitor antidepressants will have a major effect upon reducing the severity of the pain experience. At least one third of patients treated with tricylcics for neuropathic pain obtain moderate or better pain relief [1]. The use of serotonin selective reuptake inhibitors will improve mood and tolerance, but not specifically reduce pain. The effect of the antidepressants on pain is independent of any effect on depression. Studies in rats suggest that the use of amitriptyline in models of nerve injury reduce the severity and incidence of chronic

post surgical neuropathic pain [2]. In humans however there is no evidence of a reduction in incidence of pain.

The use of gabapentinoids, gabapentin and pregabalin are effective agents for treatment of neuropathic and post-surgical pain. They have analgesic and significant opioid sparing effects, that when used with opioids result in less opioid related side effects, but also provide greater sedation. The optimal dose and duration of use as well as any ability to reduce the incidence of progression to chronic pain when these agents are used is unknown [3].

The use of narcotics in various neuropathic pain states is well known to activate the NMDA dependent pain facilitatory process opposing analgesia. As such they lead to a reinforcement of central sensitization. Blockade of the NMDA receptor with agents such as N2O, ketamine or antidepressants, can be helpful in reducing the hyperalgesia in neuropathic pain states [4]. Avoidance of the use of narcotics as single agents in the treatment of neuropathic pain states may be helpful in reducing the incidence and severity of persistent pain..

Evaluation and treatment of any psychopathology and that could be contributing to the pain experience and level of suffering, is likely to improve overall function. Assessment of social factors that may be contributing to the disability is essential. Identification and correction of any social factors that may lead to increased functional disability, should be attempted as far as possible. The use of a physical general exercise program will restore function and improve psychological mechanisms leading to overall reductions in pain.

Although there are no specific interventions that at the moment will lead to a reduction in the progression from acute pain to chronic pain, there is enough evidence that reducing the suffering from the pain experience, combined with an activation program will result in improved function and reduced disability. There is some limited evidence that the use of tricyclics, ketamine and gabapentioids may reduce the level of hyperalgesia but not the incidence of chronic pain in neuropathic pain states.

REFERENCES

1. *Antidepressants for neuropathic pain. Saarto T, Wiffen PJ. Cochrane Database of Systematic Reviews 2007.*
2. *Perisurgical amitriptyline produces apreventive effect on hypersensitivity following spared nerve injury. Arsenault A, Sawynok J. Pain 2009 Sept 10.*
3. *Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Gilron J. Curr Opin Anaesthesiol 2007 Oct; 20(5): 456-72*
4. *Nitrous oxide revisited: evidence for potent antihyperalgesic properties. Richebe P et.al. Anesthesiology 2005 Oct; 103(4) :845-54*

QUESTION 3 ***COMPULSORY***

Nausea and vomiting can be common side effects of long-term treatment with opioid analgesics. Discuss the mechanisms by which opioids produce nausea and vomiting. What management options are available?

Educational Summary with Key Points:

Nausea and vomiting (N & V) are common side effects of treatment with opioid analgesics. The incidence of N & V with acute opioid use is 30-40% and with chronic use has been reported to vary between 10 and 50%. The severity of N & V can often be very distressing for patients leading to reduced quality of life, non-compliance and limitations to the adequacy of analgesia that can be obtained from this class of drugs.

Mechanisms

The vomiting centre, situated in the medulla oblongata, consists of groups of loosely organised neurones that mediate both sensory and motor control of nausea and vomiting. These neurones are stimulated or suppressed via chemoreceptors present in the vomiting centre. Input to the vomiting centre comes from 4 main areas:

1. the chemoreceptor trigger zone (CTZ)- for vomiting in particular
2. the gastrointestinal tract
3. the vestibular apparatus in the temporal lobe
4. the cerebral cortex

Opioids exert emetogenic effects in a rather complex manner, mostly via the first 3 mechanisms. They are mediated via interaction with mu, delta and kappa opioid receptors in the brain, spinal cord and peripherally. Opioid stimulation of the CTZ occurs via mu and delta receptors and, from there to the vomiting centre via dopaminergic and serotonergic pathways. This mechanism is subject to the development of tolerance with repetitive opioid administration. Central and peripheral opioid receptors are involved in inhibiting gut motility. Activation of peripheral mu opioid receptors appears to be the primary mechanism. Kappa receptor agonists have also been shown to inhibit gut motility. Inhibition of gut motility leads to gut distension, increased emptying time and constipation resulting in stimulation of visceral mechanoreceptors and chemoreceptors. Subsequent signalling to the vomiting centre is via serotonergic pathways. Most opioids stimulate the vestibular apparatus directly but the actual mechanism is not definitely known. Sensory input from here to the vomiting centre is through histaminergic H1 and muscarinic cholinergic AChm pathways. Thus, rapid movement and dehydration can stimulate nausea; and emesis is more likely in ambulant patients.

The emetogenic effect of a particular opioid may depend, therefore, on that drug's particular specificity for mu, delta or kappa opioid receptors. However, other factors that affect the incidence of emesis include inter-patient variation in these mechanisms including gender and age; variations in individual patients with time; route of opioid administration; the development of tolerance to the CTZ-mediated effects; and dose escalation as a result of the development of analgesic tolerance making emesis more likely.

Management

Management options should be determined by the likely mechanism of the N & V. They include

1. opioid drug dosing
    a. limitation of dose escalation
    b. use of novel preparations- eg transcutaneous or intrathecal delivery systems; mixed agonist/antagonist preparations
    c. opioid rotation- may be of limited benefit as the incidence of N & V varies little between opioids
    d. use of opioid-sparing adjuvants
2. taper or discontinue other emetogenic drugs
3. medication aiming to target particular mechanisms- often combinations are required and dosing is limited by tolerability of the side effects of these drugs
    a. dopamine receptor antagonists for CTZ mediated N & V
        i. phenothiazines (eg prochlorperazine)
        ii. butyrophenones (eg droperidol and haloperidol)
    b. serotonin receptor antagonists (eg ondansetron, dolasetron, granisetron, tropisetron) for CTZ mediated N & V- very good tolerability profile
    c. metoclopramide for GI side effects mediated via cholinergic mechanisms -delayed gastric emptying (signs include bloating, early satiety and postprandial vomiting) and nausea associated with constipation. Also acts on peripheral dopaminergic and serotonergic receptors plus high doses cause CTZ D2-receptor inhibition
    d. histamine antagonists (eg cyclazine) for vestibular vertigo-like symptoms as well as direct vomiting centre effects.
    e. Anticholinergic drugs (eg scopolamine) for direct vomiting centre effects
    f. Benzodiazepines – GABA agonists (eg lorazepam) targeting centrally mediated anticipatory nausea
    g. Opioid receptor antagonists – eg low dose naloxone, new mu antagonists (alvimopan, methylnaltrexone)
    h. Atypical antipsychotic, risperidone – blocks D2 and 5-HT2 receptors has been used for refractory N & V in advanced cancer patients

4. non-pharmacologic methods
    a. access to fresh air
    b. limiting dietary intake of triggering foods (eg sweet, salty, fatty or spicy)
    c. distraction
    d. relaxation therapy
    e. multi-disciplinary cognitive therapies (exercise, relaxation, sleep management, pain education and cognitive restructuring)

REFERENCES

Porreca, F, Ossipov, MH (2009) Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications and management options Pain Medicine 10(4);654-662

Suggested MARKING GUIDE

	Mark
General comment about incidence and impact	1
Mechanisms 1. mention vomiting centre as key area 2. mention the 4 areas that can influence the vomiting centre 3. mention opioids, their effect on receptors and how they may affect the 3 key areas (CTZ, GI tract and vestibular) 4. comment about long-term opioid administration issues	4
Management 1. opioid drug related management 2. antiemetics 3. non-pharmacological treatments 4. reduce/avoid other emetogenic medications	4
Global	1
TOTAL	10

QUESTION 4 ***COMPULSORY***

Describe the clinical indicators of central sensitisation and discuss potential mechanisms.

Answer:

Introduction:

"Central Sensitisation " is a commonly used term that denotes amplification of pain impulses within the spinal cord and brain.
At physiological level it denotes a critically important concept in the understanding of pain transmission where the actual experience of pain is not always proportional to the pain stimulus.
Central sensitization corresponds to an enhancement in the functional status of neurons and circuits in nociceptive pathways throughout the neuraxis caused by increases in membrane excitability, synaptic efficacy, ora reduced inhibition. The net effect is that previously subthreshold synaptic inputs are recruited to generate an increased or augmented action potential output, a state of facilitation, potentiation, or amplification.

Clinical indicators:
Clinical signs and symptoms are extremely variable.
Three major components can be distinguished:

(1) Sensory abnormalities, including spontaneous burning pain, hyperalgesia, and allodynia,

(2) Vascular and sweating abnormalities, oedema and trophic changes in skin, subcutaneous tissues, joints, and bone,

(3) Motor abnormalities, including impairment of active and passive function, tremor, or dystonia.

Patients with widespread pain or fibromyalgia syndrome have many symptoms besides musculoskeletal pain: e.g.

- Fatigue,
- Sleep difficulties,
- A swollen feeling in tissues,
- Paraesthesia,
- Cognitive dysfunction,
- Dizziness
- Symptoms of overlapping conditions
  - Irritable bowel syndrome,
  - Headaches
  - Restless legs syndrome.
  - Anxiety, stress and depression are also present in 30–45% of patients.

Central sensitization is not unique to fibromyalgia; it also occurs in other painful conditions such as irritable bowel syndrome, overactive bladder, TMJ syndrome, idiopathic low back pain, vulvodynia, multiple chemical sensitivity.
There is evidence for central sensitization in these conditions, but further studies are needed.

- Other factors that may contribute to symptoms :

    - Endocrine dysfunction,
    - Psychosocial distress,
    - Trauma
    - Disrupted sleep.

- Differences in skin temperature and “the ischemia test” may be used as diagnostic criteria
- Sympathetic blocks relieve pain and other symptoms in a subgroup of patients (sympathetically maintained pain, SMP).
- Primary hyperalgesia in musculoskeletal tissues can be experimentally induced by infusion of different algogenic substances (nerve growth factor, or glutamate).

Evaluation of a patient presenting with widespread pain includes history and physical examination to diagnose both pain patterns and associated or concomitant conditions.
Suspicion of potential central sensitisation indicates need to consider pre-emptive analgesia, trials of NMDA receptor antagonists, coxibs and gabapentin

Potential mechanisms

Introduction:

- A complex perception influenced by prior experience and by type of noxious stimulus
- Input via A-delta (fast conducting) and C-fibres (unmyelinated, slow conducting)
- Peripheral fibres synapse at dorsal horn -- many neurotransmitters modulate post synaptic responses
- Transmission to supra-spinal sites (thalamus, anterior cingulate cortex, insular cortex & somatosensory cortex
- Enhanced responsiveness of nociceptive neurons in the central nervous system,
  e.g., during inflammation or trauma
- The simplest CNS plasticity is via habituation following repeated noxious stimuli (decreased response) or sensitisation (increased response)
- Prolonged or intense dorsal horn neuronal activity may lead to increased neuronal responsiveness (central sensitisation)
    - These changes cause alterations of chemical, electrophysiological and pharmacological brain responses
- Changes cause exaggerated perception of painful stimuli (hyperalgesia)
- Perception of innocuous stimulus as painful (allodynia)
- Referred pain and hyperalgesia across multiple segments.

- Note: sensitisation of nociceptors is a well established peripheral mechanism leading to allodynia and hyperalgesia,

Mechanism:

- exact mechanisms not fully clarified but include:

1. **Wind-up**

- Temporal summation (wind-up) Central spinal mechanisms with repetitive noxious stimuli allow a slow temporal summation experienced as increased pain

- C- fibre stimulation results in progressive increase in discharges from second and third order neurons

- Transmitted through unmyelinated C-fibres to NMDA second-order receptors

- NMDA activation induces calcium entry into the dorsal horn neurons
- Calcium entry into sensory neurons in the dorsal horn induces activation of nitric oxide (NO) synthetase, leading to the synthesis of NO.

NO can affect the nociceptor terminals and
- enhance the release of sensory neuropeptides in particular, substance P from presynaptic neurons,
- therefore contributing to the development of hyperalgesia and maintenance of central sensitization.

Substance P is an important nociceptive neurotransmitter:
- Lowers the threshold of synaptic excitability, resulting in the unmasking of normally silent interspinal synapses and sensitization of second-order spinal neurons

- Substance P can extend for long distances in the spinal cord and sensitize dorsal horn neurons at a distance from the initial input locus. This results in an expansion of receptive fields and the activation of neurons by non-nociceptive afferent impulses

- Intradermal capsaicin in humans causes pain, primary hyperalgesia, and secondary mechanical hyperalgesia and allodynia.
  Secondary mechanical allodynia is actively maintained by central mechanisms.
  Parallel changes occur in the responses of primate spinothalamic tract cells & in rat behaviour.
- Release of endogenous substances including opioids, cannabinoids and amines are replaced to counteract the development of central sensitisation

- Wind-up can be elicited in human patients if identical nociceptive stimuli are applied to the skin or muscles more often than once every 3 s
  When C-fibres are electrically stimulated at a frequency between 0.3 and 3 Hz, some spinal neurons respond to the first 10–30 stimuli with an increasing number of actions potentials (“wind-up”), often followed by a decrease in number of action potentials per stimulus This is a normal coding feature of some nociceptive spinal dorsal horn neurons and not per se a sign of sensitisation.

- Wind-up has been demonstrated to result from a central rather than a peripheral nervous system mechanism, because the input from C nociceptors has been shown to decline or stay the same with stimulus repetition

2. Endogenous pain modulatory systems:

- **Dysregulation of descending inhibitory pathways**
- **Up-regulation of facilitatory modulation**
- **Disruption of descending inhibitory pathways to activated dorsal horn neurones results in generation of more rapid pain signals leads to hyperalgesia across multiple spinal segments**

Central sensitization, in contrast to peripheral sensitization, co-opts novel inputs to nociceptive pathways
including those that do not normally drive them, such as large low-threshold mechanoreceptor myelinated fibers to produce Ab fiber–mediated pain.376 It also produces pain hypersensitivity in non-inflamed tissue by changing the sensory response elicited by normal inputs and increases pai sensitivity long after the initiating cause may have disappeared and when no peripheral pathology may be present.

About 30–40% of the neurons in spinal laminae I and II are inhibitory and an increase in the responsiveness of inhibitory nociceptive neurons may lead to a stronger feed-back inhibition and thus anti-nociception rather than to allodynia or hyperalgesia

- Forebrain centres exert significant influences on brainstem nuclei (behavioural evidence)
- Alteration of pain inhibitory and facilitatory centres in the brain stem (dorsolateral funiculus)
- Expansion of dorsal horn nociceptive receptive fields
- Serotonergic inhibitory neurones are inactivated resulting in pain hypersensitivity
- Selective attention to relevant pain stimuli activates facilitation and maintains persistent pain after actual tissue damage or inflammation has ceased.

<u>Experimental studies that confirm central sensitisation:</u>

- Qualitative differences in pain *(QST and pain scale differences)*
- Deficient pain modulation in response to repeated thermal stimuli *(inhibition of dorsal horn neuron excitability by persistent stimulation of type A myelinated axons)*
- Hyper-responsive somatosensory induced potentials
- Secondary hyperalgesia on electrocutaneous stimulation
- Elevated levels of substance P in CSF
- Elevated levels of nerve growth factor
- Positive response to an NMDA receptor antagonist *(IV or SC ketamine)*
- Experimentally induced central hyperexcitability *(increased temporal summation)*
- Neurogenic Inflammation *(release of histamine, substance P & inflammatory cytokines from nociceptors in the skin / increased levels of mRNA for inflammatory cytokines (IL-1, TNFa and IL-6) in skin)*
- Functional MRI
- Spinal Flexion Reflex *(objective evidence for spinal cord hyperexcitability in patients with chronic pain)*

Particular cognitive styles and personalities may be associated with amplification of pain

- Somatisation
- Catastrophising
- Hypervigilance

- Therefore, behavioural and cognitive therapies act via descending pathways to effect synaptic transmission in the spinal cord and have capacity to prevent or reverse long-term changes in synaptic strength in pain pathways.
- Even though various inflammatory and musculoskeletal disorders and neuropathic pain disorders have similar mechanisms leading to central sensitisation, some differences occur -- these differences may be important in relation to potential treatments.
- Hyperalgesia depends mainly on peripheral input.

REFERENCES

1. *Wall and Melzak's Textbook of Pain 5th Edition (2006) pp. 22, 28, 92, 224,674,822. McMahon SB, Koltzenburg M. Eds.*
2. *Sandkuhler , J & Ruscheweyh,R. Opioids and central sensitisation: I. Pre-emptive analgesia. European Journal of Pain (2005) 145–148*
3. *Meeus, M & Nijs, J, Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome Clinical Rheumatology (2007) 26:465 -473.*
4. *Winkelstein BA (2004) Mechanisms of central sensitization, neuroimmunology and injury biomechanics in persistent pain: implications for musculoskeletal disorders. J Electromyogr Kinesiol 14:87–93*
5. *Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD (2001) Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 91:165–175*
6. *Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L (1998) Hyperexcitability in fibromyalgia. J Rheumatol 25:152–155*
7. *Julien N, Goffaux P, Arsenault P, Marchand S(2005) Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 114:295–302*
8. *Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden AM, Radanov BP (2001) Central hypersensitivity in chronic pain after whiplash injury. Clin J Pain 17:306–315*
9. *Cervero F, Laird JM. Mechanisms of touch-evoked pain (allodynia): a new model. Pain 1996;68:13–23.*
10. *Cervero F, Laird JM, Garci, Nicas E. Secondary hyperalgesia and presynaptic inhibition: an update. Eur J Pain 2003;7:345–51.*
11. *Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–8.*
12. *Rowbotham MC, et al. Role of central sensitization in chronic pain: Osteoarthritis and rheumatoid arthritis compared to neuropathic pain. Proceedings of the 11th World Congress on Pain; 2006:231-249*
13. *Romanelli P,Esposito V. Neurosurg Clin N Am 2004;15:257-268.*

14. *Graven-Nielsen T, et al. Central sensitization, referred pain and deep tissue hyperalgesia in musculoskeletal pain.Proceedings of the 11th World Congress on Pain; 2006:217-230.*
15. *Woolf CJ, Mannion RJ. Neuropathic pain: aetiology,symptoms, mechanisms, and management. Lancet 1999;353:1959-1964.*
16. *Woolf CJ. Windup and central sensitization are not equivalent. Pain1996;66:105–8.*
17. *Latremoliere, A and Woolf, CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural PlasticityThe Journal of Pain, Vol 10, No 9 (September), 2009: pp 895-926*

Guide:

Marks for brief discussion of:
Symptoms

- Three major symptom patterns
    - Sensory
    - Motor
    - Autonomic
- Associated symptoms
- Need to consider comorbidities
- Cortical and emotional influences
- Endocrine and other influences
- Discussion of fibromyalgia
- Discussion of pre-emptive analgesia

Mechanisms

- pre-and post-synaptic components
- Fibre types
- Neuroplasticity
- Substance P/NMDA/serotoninergic transmission/nitric oxide/calcium channels
- Expansion of receptive fields
- Wind-up
- Up regulation of facilitators
- Down regulation of inhibitors

QUESTION 5 ***COMPULSORY***

Discuss the psychosocial factors that have been demonstrated to influence outcomes of lumbar spine surgery.

In the study of factors that predict the outcome of any type of therapy it is essential that the independent variables be assessed, or measured, prospectively rather than retrospectively. It is also essential that the "outcomes" or end-points be defined prospectively and not after the treatment, in this case lumbar spine surgery, had been completed or performed.

In the assessment of the results of lumbar spine surgery it is necessary to define the categories of outcome, for example:

"good outcome",
"fair outcome"
"poor outcome".

It is also necessary to determine the specific measures of outcome that will be used, such as:

pain severity report,
functional status (self-care, fanctional activity, vocational retraining, return to work),
continued use of medications,
further health care utilisation,
patient satisfaction rating,
global rating of mood state (depression, anxiety, anger).

This question asks specifically about relevant psychosocial predictive factors, and therefore the medical factors will not be enumerated although it needs to be noted that these have been demonstrated to be of importance and that, in particular, lumbar spine surgery should not be undertaken for the purpose of pain relief only and that it should be undertaken only if there are objective signs of pathology that is amenable to surgical correction.

In relation to psychosocial factors that generally have been shown to influence the outcomes of lumbar spine surgery, these can be divided into the psychological and the social. Psychological factors can be further divided into those related to personality (trait variables), cognition, and past psychological or psychiatric problems, and those reflecting current emotional state (state variables).

Personality traits that have been shown to be associated with poor surgical outcomes, which can be assessed using psychometric instruments, include:

increased scores on the MMPI Hy and Hs scales (high pain sensitivity),
increased score on the MMPI Pd scale (anger and problems with authority figures),
increased score on the MMPI Pt scale (agitation and worry),
somatic anxiety.

Cognitive factors associated with poor surgical outcomes include:

poor coping skills,
low self-reliance,
low pain control.

Past history that is associated with poor surgical outcomes includes:
- history of physical and sexual abuse, particularly during childhood,
- past history of substance abuse,
- past history of mental disorder or other significant psychological difficulties.

State variables that are associated with poor surgical outcomes include:
- depression,
- anxiety.

Some studies have shown that hostility was not associated with outcome following lumbar surgery.

Social factors that are associated with poor outcomes following lumbar spine surgery include:
- unemployment,
- receipt of workers' compensation or other social security benefits,
- pending litigation or application for disability benefits,
- job dissatisfaction and anger at employer,
- heavy job demans,
- reaction of spouse to injury and marital dissatisfaction,
- smoking,
- older age,
- English proficiency (in an Ontario, Canada, study).

Recent review by Celestin et al concluded that there is insufficient empirical evidence that psychosocial screening prior to lumbar spine surgery helps to improve treatment outcome, but that the literature suggests that factors such as depression, anxiety, poor coping and somatisation are important predictors of poor outcome.

REFERENCES

1. *Block AR. Presurgical Psychological Screening in Chronic Pain Syndromes. Lawrence Erlbaum. Associates: Mahwah (NJ), 1996.*
2. *Carreon LY, et al. Are preoperative health-related quality of life scores predictive of clinical outcomes after lumbar fusion? Spine 2009; **34**:725-30.*
3. *Celestin J, et al. Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis. Pain Medicine 2009; **10**:639-53.*
4. *Dzioba RB, Doxey NC. A prospective investigation into the orthopaedic and psychologic predictors of outcome of first lumbar surgery following industrial injury. Spine 1976; **9**:614-23.*
5. *Mannion AF, Elfering A. Predictors of surgical outcome and their assessment. Eur Spine J 2006; 15:S93-108.*
6. *Sorenson LV, Mors O, Skovlund OA. A prospective study of the importance of psychological and social factors for the outcome after surgery in patients with slipped lumbar disk operated upon for the first time. Acta Neurochir 1987; 88:119-25.*
7. *Trief PM, Grant W, Fredrickson B. A prospective study of psychological predictors of lumbar surgery outcome. Spine 2000; **25**:2616-21.*
8. *Trief PM, Ploutz-Snyder R, Fredrickson BE. Emotional health predicts pain and function after fusion:a prospective multicenter study. Spine 2006; **31**:823-30.*
9. *Uomoto JM, Turner JA, Herron LD. Use of the MMPI and MCMI in predicting outcome of lumbar laminectomy. J Clin Psychol 1988; 44:191-7.*
10. *Vaccaro AR et al. Predictors of outcome in patients with low grade spondylolisthesis. Spine 1997; 22:2030-5.*

QUESTION 6 ***NON COMPULSORY***

Discuss the pharmacogenomics in the management of pain.

Definition

Pharmacogenomics is the whole genome application of pharmacogenetics that examines the single gene interactions with drugs. It deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms (SNPs) with a drug's efficacy or toxicity. Impressive interindividual variability has been documented in experimental and clinical responses to analgesic manipulations as well, including to opioids, placebo, and non-steroidal anti-inflammatory drugs. (1) Pharmacogenomics aims to develop rational means to optimise therapeutic strategies, based on the patients' genotype, to ensure maximum efficacy with minimal adverse effects.

Prevention of Pain

Complete prevention of pain has so far been seen in six distinct rare hereditary syndromes. These are the 'channelopathy-associated insensitivity to pain', caused by 13 currently identified variants in the SCN9A gene coding for the alpha-subunit of the voltage-gated sodium channel, and five maladies belonging to the hereditary sensory and autonomic neuropathy (HSAN) I-V syndromes, caused by various mutations in several genes. (2)

Reduction of pain

Reduced pain in the average population has been associated with frequent variants in the micro-opioid receptor gene (OPRM1), catechol-O-methyltransferase gene (COMT), guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia gene (GCH1), transient receptor potential cation channel, subfamily V, member 1 gene (TRPV1) or the melanocortin-1 receptor gene (MC1R). (3)

Micro-opioid receptor gene (OPRM1)
Several reports have confirmed the functional importance of the mu-opioid receptor variant N40D (i.e. an asparagine instead of an aspartate as the 40th amino acid of the receptor protein) coded by the single nucleotide polymorphism (SNP) 118A > G of the OPRM1 gene on chromosome 6q24q25. (4) Prior work indicates that the A118G SNP is associated simultaneously with reduced acute pain responsiveness (4,5) and increased exogenous opioid analgesic requirements. (6,7)

Catechol-O-methyl transferase gene

The influence of the polymorphic catechol-*O*-methyl transferase (*COMT*) gene located on chromosome 22 (22q11.21) to pain has been an active area of investigation. Haplotypes composed of four COMT SNPs with high COMT activity are assosciated with low pain sensistivity to mechanical and thermal stumuli.(8)

Guanosine triphosphate cyclohydrolase 1 (GCH1) gene
In humans, a haplotype of the *GCH1* gene on chromosome 14q22.1-q22.2 found at an allelic frequency of 15.4% is significantly associated with reduced sensitivity to pain following discectomy for radicular pain.(9)

Enhancing analgesic drugs

Melanocortin-1 receptor gene

Subjects carrying melanocortin-1 receptor gene (*MC1R*) variants on chromosome 16q24.3 coding for amino acid substitutions known to abolish MC1R functionality (R151C, R160W and D294H), possess a red-hair fair-skin phenotype. (2) There is a significantly greater analgesic effect in female subjects with two variant alleles compared with those with zero or one allele. (10)

Drug Metabolism

Genetic variations can occur during uptake, transport, at the effector site, and during the metabolism and excretion of a drug. With the opioids, pharmacogenomics can influence their response (efficacy, toxicity, pharmacokinetics, metabolism, transport) and contribute to intersubject and interpatient variability.

Cytochrome P450-2D6

The polymorphic cytochrome P450 enzymes metabolise numerous drugs and show inter-individual variability in their catalytic activity. More than 100 distinct allelic variants for CYP2D6 are known. (11) Individuals can be extensive metabolisers, intermediate metabolisers, or poor metabolisers. Poor metabolisers display a frequency of about 7–10% in Caucasian populations.(12) Three to five per cent of the Caucasian population are ultrarapid metabolisers, in whom therepeutic effects cannot be obtained with conventional doses. (12,13)

Codeine

The o-demethylation of codeine to the active metabolite, morphine depends on CYP2D6 activity. (11) Seven to ten percent of a Caucasian population have two poor metaboliser-associated polymorphisms, resulting in an almost complete absence of enzyme activity. (12,14)

Tramadol

Tramadol produces analgesia by a synergistic action of its two enatiomers. O-demethylation of tramadol to the active metabolite, (+)-*O*-demethyltramadol (ODT or M1), requires CYP2D6 for its formation. Genetically determined poor metabolisers of CYP2D6 experience reduced analgesia owing to deficient enzyme activity and negligible formation of (+) ODT.(14,15)

Methadone

Genetic polymorphisms in genes coding for methadone-metabolizing enzymes, transporter proteins (p-glycoprotein), and mu-opioid receptors may explain part of the observed inter-individual variation in the pharmacokinetics and pharmacodynamics of methadone. (16) The effects of a 30-fold variation in CYP450 enzyme activity between patients (fast, medium or slow methadone metabolisers), explains the wide range of half-lives (5–150 hours), and in part, the highly variable clinical responses to methadone loading.

NSAIDs

NSAID's like ibuprofen, naproxen and piroxicam are metabolised by CYP2C9. (17) Between 1-3% of Caucasians are poor metabolisers.

Antidepressants

In antidepressant drug treatment, most drugs are metabolized via the polymorphic cytochrome P450 enzyme CYP2D6.(18) Huge differences in pharmacokinetic parameters have been consistently shown for many tricyclics, some SSRIs, and other antidepressant drugs. To date, the most promising strategy in clinical practice appears to incorporate testing of functional CYP450 gene variants (CYP1A2, CYP3A4, CYPD26 and CYP2C19) to avoid over- or under-dosing in poor or rapid metabolisers, respectively.(19)

Conclusion

Knowledge of genetic factors will lead to the designing of more effective pain medications with lower adverse effect profiles. In the best of all possible worlds, researchers would proceed by identifying relevant genes/proteins in humans (thereby proving their relevance), studying the roles played by these molecules in animal models, and then using this information to provide better treatments for those in pain. (1)

REFERENCES

1. *Lacroix-Fralish ML, Mogil JS. Progress in genetic studies of pain and analgesia. Annu Rev Pharmacol Toxicol 2009;49:97-121.*
2. *Oertel B, Lötsch J. Genetic mutations that prevent pain: implications for future pain medication. Pharmacogenomics 2008;9(2):179-94.*
3. *Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J Clin Invest 2007;117(12):3603-9.*
4. *Lotsch J, Stuck B, Hummel T. The human mu-opioid receptor gene polymorphism 118A > G decreases cortical activation in response to specific nociceptive stimulation. Behav Neurosci 2006;120:1218–24.*
5. *Fillingim RB, Kaplan L, Staud R, et al. The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. J Pain 2005:6:159–67.*
6. *Klepstad P, Rakvag TT, Kaasa S, et al. The 118 A>G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004;48:1232–9.*
7. *Bruehl S, Chung OY, Burns JW. The mu opioid receptor A118G gene polymorphism moderates effects of trait anger-out on acute pain sensitivity. Pain 2008;139(2):406-15.*
8. *Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14(1):135-43.*
9. *Tegeder I, Adolph J, Schmidt H, et al. Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. Eur J Pain 2008;12(8):1069-77.*
10. *Mogil JS, Wilson SG, Chesler EJ, et al. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci U S A 2003;100(8):4867-72.*
11. *Stamer UM, Stüber F. Genetic factors in pain and its treatment. Curr Opin Anaesthesiol 2007;20(5):478-84.*

12. *Stamer UM, Musshoff F, Kobilay M, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82(1):41-7.*
13. *Sachse C, Brockmöller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 1997;60(2):284-95.*
14. *Stamer UM, Lehnen K, Höthker F, Bayerer B, Wolf S, Hoeft A, Stüber F. Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003; 105: 231–8.*
15. *Poulsen, L., Arendt-Nielsen, L., Brøsen, K. & Sindrup, S. The hypoalgesic effect of tramadol in relation to CYP2D6. Clin Pharmacol Ther 1996;60:636–44.*
16. *Li Y, Kantelip JP, Gerritsen-van Schieveen P, Davani S. Interindividual variability of methadone response: impact of genetic polymorphism. Mol Diagn Ther. 2008;12(2):109-24.*
17. *Rollason V, Samer C, Piguet V, et al. Pharmacogenetics of analgesics: toward the individualization of prescription. Pharmacogenomics. 2008;9(7):905-33.*
18. *Kirchheiner J, Seeringer A. Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. Biochim Biophys Acta 2007;1770(3):489-94.*
19. *Tiwari AK, Souza RP, Müller DJ. Pharmacogenetics of anxiolytic drugs. J Neural Transm 2009;116(6):667-77.*

QUESTION 7 ***NON COMPULSORY***

You are a member of an acute pain service. The surgeon is keen for a patient undergoing an open hemicolectomy to be part of their 'fast-track' program, with early discharge planned at 4 days.

Discuss your approach to pain management in this situation.

'Fast-track' protocols for surgery aim to accelerate a patient's recovery and shorten hospital stay as a result of:

- optimisation of perioperative care
- aggressive postoperative rehabilitation
  - including early ambulation
  - early return to a normal diet.

A recent meta-analysis (Gouvas et al 2009) which analysed RCTs and non-RCTs separately as well as combined, reported that use of

- fast-track protocols after colorectal surgery led to:
  - Reductions in primary length of hospital stay (days in hospital until time of discharge
  - Total length of hospital stay (primary stay plus any readmissions),
  - similar readmission and mortality rates,
  - lower patient morbidity.

'Fast-tracking' requires implementation of an evidence-based perioperative patient care program that reduces the time to discharge home as well as resumption of normal activities

<u>Adequate pain relief is only one part of fast-track surgery and must be integrated with all other components of the program.</u>

Pain management plans allow:

- Early mobilisation,
- Early return of bowel function
- Adequate oral intake of food & fluids;
- Discharge analgesia will also be important.

For such a program to work there must be good cooperation and communication between all groups (acute pain service, surgeons nurses, physiotherapists) and the development of agreed protocols. The patient and their family must also be involved

Key elements:

- Good pain relief aimed at early mobilisation and early return of bowel function
- Prevention and early and effective treatment of postoperative nausea and vomiting to encourage early and adequate oral intake
- Minimisation of other adverse effects of pain relief
- Communication with surgical team, nursing staff and physiotherapists (including participation in, and the development of, institutional fast-track protocols)
- Involvement of Acute Pain Service

- Effective pain relief after discharge
- Patient education

1. Options for Pain Relief
Pain relief needs to allow for early mobilisation and early return of bowel function.
Most studies of fast-track colorectal surgery use thoracic epidural analgesia as key element.

- However, in all patients, the risk-benefit of this technique needs to be assessed. Epidural analgesia may not be considered warranted in younger and healthier patients and may be contraindicated in others.
- If opioids are to be the main form of analgesia, the addition of 'opioid-sparing' adjuvants is usually advocated.

(a) Epidural analgesia
After colorectal surgery, epidural analgesia in comparison to systemic opioid analgesia reduced pain scores and duration of ileus, but had no effect on hospital stay

- (this meta-analysis did not look for differences between fast-track and non-fast-track care); rates of pruritus, urinary retention and hypotension were increased (Marret et al, 2007).

Epidural analgesia using thoracic placement of catheter

- Avoids motor & sensory blockade of legs
    - *Use low concentration usually with low-dose opioid such as fentanyl. (Fentanyl has some effect on bowel motility but pain relief is not significantly better with local anaesthetic alone)*
- Minimises risk of hypotension (if occurs treat appropriately)
- Minimises volume of epidural solution needed to get good pain relief
- Results in better return of bowel function compared with lumbar epidural

(b) Continuous local anaesthetic wound infusions

- Not as effective as epidural analgesia, but no effect on motor function or blood pressure.

One recent meta-analysis reviewed outcomes following postoperative analgesia after a variety of different operations (cardiothoracic, general, gynaecology-urology and orthopaedics) using continuous local anaesthetic wound infusions (Liu et al, 2006).
Analyses were performed for all surgical groups combined and for the four subgroups. While there were some minor variations between the subgroups, the results overall showed that this technique led to reductions in pain scores (at rest and with activity), opioid consumption, PONV and length of hospital stay (orthopaedic surgery only).

- Pre-peritoneal infusion of ropivacaine after colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function (Beaussier et al, 2007).

(c) Opioid analgesia
Depending on age and cognitive state of patient : offer patient-controlled analgesia or intermittent opioid injections.

- Better pain relief with PCA compared with conventional opioid analgesia but no difference in adverse effects (*except itching*), including effect on bowel motility (Hudcova et al 2006)
- No difference in incidence of adverse effects, including bowel motility, between different mu-agonist opioids
- Tramadol has less effect on bowel motility but limit to the dose that can be used (600 – 1000 mg IV depending on institution) and so it may be inadequate as the sole analgesic agent; given with morphine it is opioid-sparing but infra-additive (Marcou et al, 2005; Thevenin et al, 2008). There are also more contraindications to the use of tramadol (eg concurrent SSRI administration)

(d) Opioid-sparing systemic adjuvant analgesics

PONV is related to opioid administration & is dose-dependent. (Marret et al, 2005).

- drugs used as components of multimodal analgesia and which are opioid-sparing may also reduce PONV.

Opioid-sparing and a reduction in PONV has been shown with concurrent administration of:

- *Gabapentin* (Tiippana et al, 2007),
- *Non-selective nsaids* (Elia et al, 2005; Marret et al, 2005)
- *Ketamine* (Bell et al, 2006).
- Opioid-sparing with no decrease in PONV was reported for *paracetamol* and *COX2-selective NSAIDs* (Elia et al, 2005; Remy et al, 2005).

Specific evidence of effect on bowel motility is limited.

Ketorolac added to tramadol PCA did not improve pain relief or alter the incidence of side effects; however it was opioid-sparing and led to earlier return of bowel function after colorectal surgery (Chen et al, 2009).

COX2-selective NSAIDs may lead to an increased rate of anastomotic breakdown, but more investigation of this is needed (Holte et al 2009).

Clonidine is opioid-sparing but mainly in doses that also lead to excessive sedation +/- hypotension & constipation, so not routinely recommended.

2. Prevention and Early and Effective Treatment Of Ponv

- give antiemetics during surgery
- Treat PONV immediately
  - Good evidence of benefit for droperidol, $5HT_3$ antagonists, dexamethasone (single dose) and some others
  - Good evidence for combination therapy being more effective
  - No good evidence of benefit for metoclopramide although pro-kinetic effect may be useful in this circumstance

3. Patient Education

Patient information, starting before admission to hospital for surgery, is very important to the success of fast-track programs. Detailed instructions are needed for the preoperative, in-hospital and after-discharge phases of treatment so that the patient and their family know what each stage of treatment entails.

After discharge support should also be available to all patients.

4. Communication With Surgical Team, Nursing Staff And Physiotherapists

Multidisciplinary collaboration is essential. Acute pain service team must participate in the development of, and use of, institutional fast-track protocols.

- includes daily care maps and well-defined discharge criteria.
- regular communication with other members of the treating team including physiotherapists).
- Adequate information to the patient's general practitioner about fast-track programs as they may be the called by the patient or their family.

5. Effective Pain Relief After Discharge

Inadequate pain relief after discharge from hospital is one of the most common reasons for readmission after day surgery.

- may still need oral opioids but minimise where possible
- continue to use 'opioid-sparing' adjuvant analgesics– eg paracetamol, NSAIDs, tramadol

REFERENCES

1. *Baldini G, Carli F. Anesthetic and adjunctive drugs for fast-track surgery. Curr Drug Targets. 2009 Aug;10(8):667-86.*
   Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbølle P, Hendel HW, Rosenberg J, Kehlet H.
   Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition.Br J Surg. 2002 Apr;89(4):446-53.
2. *Beaussier M, El'Ayoubi H, Schiffer E et al*
   Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. Anesthesiology 2007; 107(3): 461-8.
3. *Bell RF, Dahl JB, Moore RA et al*
   Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006 (1): CD004603.
4. *Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P.*
   Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology. 2002 Sep;97(3):540-9.
5. *Chen JY, Ko TL, Wen YR, Wu SC, Chou YH, Yien HW, Kuo CD.*
   Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel function in colorectal surgery patients: a prospective randomized double-blinded study. Clin J Pain. 2009 Jul-Aug;25(6):485-9.
6. *Elia N, Lysakowski C & Tramer MR*
   Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005; 103(6): 1296-304.
7. *Gouvas N, Tan E, Windsor A, Xynos E, Tekkis PP*
   Fast-track vs standard care in colorectal surgery: a meta-analysis update. Int J Colorectal Dis. 2009 Oct;24(10):1119-31. Epub 2009 May 5.
8. *Holte K, Andersen J, Jakobsen DH, Kehlet H.*
   Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery. Br J Surg. 2009 Jun;96(6):650-4.
9. *Hudcova J, McNicol E, Quah C et al*
   Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2006 (4): CD003348

10. *Ionescu D, Iancu C, Ion D, Al-Hajjar N, Margarit S, Mocan L, Mocan T, Deac D, Bodea R, Vasian H. Implementing Fast-Track Protocol for Colorectal Surgery: A Prospective Randomized Clinical Trial. World J Surg. 2009 Aug 26.*
11. *Liu SS, Richman JM, Thirlby RC et al*
    Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg 2006; 203(6): 914-32
12. *Marcou TA, Marque S, Mazoit JX et al*
    The median effective dose of tramadol and morphine for postoperative patients: a study of interactions. Anesth Analg 2005; 100(2): 469-74
13. *Marret E, Kurdi O, Zufferey P et al*
    Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005; 102(6): 1249-60.
14. *Marret E, Remy C & Bonnet F*
    Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg 2007; 94(6): 665-73.
15. *Remy C, Marret E & Bonnet F*
    Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005; 94(4): 505-13.
16. *Serclová Z, Dytrych P, Marvan J, Nová K, Hankeová Z, Ryska O, Slégrová Z, Burešová L, Trávníková L, Antoš F.*
    Fast-track in open intestinal surgery: Prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456).Clin Nutr. 2009 Jun 15.
17. *Thevenin A, Beloeil H, Blanie A et al*
    The limited efficacy of tramadol in postoperative patients: a study of ED80 using the continual reassessment method. Anesth Analg 2008 106(2): 622-7.
18. *Tiippana EM, Hamunen K, Kontinen VK et al*
    Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 2007; 104(6): 1545-56.
19. *Kehlet, H ,WilmoreD W.*
    Evidence-Based Surgical Care and the Evolution of Fast-Track SurgeryAnnals of Surgery • Volume 248, Number 2, August 2008
20. *White, PF, Kehlet, H, Neal, JM, Schricker,T, Carr, DB, Carli, F. (Fast-Track Surgery Study Group)*
    The Role of the Anesthesiologist in Fast-Track Surgery: From Multimodal Analgesia to PerioperativeMedical Care . Anesth Analg 2007;104:1380 –96

QUESTION 8 ***NON COMPULSORY***

What are the methods available to prevent the evolution to and severity of Post Herpetic Neuralgia?

Epidemiology:

Currently most Australians have been infected with varicella zoster virus (VSV).
They therefore are at risk of developing AHZ and then going on to develop PHN.
Overall 10% of patients with AHZ will go on to develop PHN, but the incidence increases with age. By age of 70, approximately 50% will develop PHN.
So a two-pronged attack is required to try to reduce the incidence and severity of PHN.

Prevention of Acute herpes Zoster (AHZ).

1. Immunization in childhood.
2. Re-exposure is important to boost the cell-mediated immunity.
3. Primary infection produces long-term immunity. Protection from reactivation depends on intact cell-mediated immunity. This declines with age, with certain diseases (HIV, some malignancies) and with immunosuppressive therapies (organ transplant, chemotherapy and steroids)
4. Adult immunization will become increasingly important. With childhood immunization, the pool of infection within the community will decrease. This may increase the risk of AHZ within the community, in the short term, as individuals previously infected with the Herpes Zoster virus (childhood chicken pox) will not have their immunity “boosted” by multiple re-exposures. Until the cohort of immunized children reach adulthood, we can expect the incidence of AHZ may increase.
5. Role of live attenuated VZV vaccine.
    a. “Prevents” HZ in 60-69 year olds, and either prevents or attenuates HZ in the elderly.
    b. Clinicians should recommend vaccine at all immunocompetent individuals aged 60 years or older.
    c. In Australia it is indicated to prevent HZ and PHN, and reduce acute and chronic pain in individuals aged over 60.

Prevent PHN after an episode of Acute Herpes Zoster.

Principle goal of treatment of HZ is to reduce pain in the immunocompetent patient and cease viral replication in the immunocompromised patient and those with ophthalmic HZ.
All patients need a medical and psychological assessment to confirm the diagnosis and document the physical and psychological context in which this disease develops.

1. Patients who develop AHZ need to be recognised quickly and treated early and aggressively to try to reduce the incidence and severity of PHN.
2. Antiviral medication:
    a. The antiviral medications (valaciclovir, famciclovir, acyclovir) do reduce much (but not all) of the morbidity associated Herpes Zoster. They accelerate the resolution of acute pain and skin lesions, and reduce the duration and possibly the incidence of PHN.

b. Antivirals work best when prescribed within 72 hours of the rash onset.Current evidence suggests benefit may extend beyond this time period, so if the pain is severe or lesions are progressive it is still recommended to trial the antivirals.
c. As increasing age, the presence (and severity) of prodromal pain, and the severity of acute zoster pain all "predict" that PHN will develop, antivirals should be prescribed in these individuals.
d. Those individuals aged over 50, or if immuno-compromised or with ophthalmic zoster, could also benefit.
e. They are still under prescribed in Australia.

3. Corticosteroids (oral), tapering over 3 weeks, can reduce the acute inflammatory phase, if used in conjunction with the antivirals. They do not prevent PHN.
4. Analgesics:
    a. Zoster associated pain should be treated early and aggressively as evidence suggests it is more difficult to treat once established.
    b. The more severe the acute pain, the higher the risk of PHN, suggesting early aggressive treatment is appropriate.
    c. Start with simple analgesics and move up to stronger opioids if necessary.
5. Tricyclic antidepressants:
    a. Amitriptyline (25mg nocte), decreased PHN at 6 months by 50%.
6. Gabapentin and pregablin have been shown to be useful in patients with neuropathic pain including PHN. They may if used early with antivirals decrease the incidence of PHN.
7. Neural blockade. Sympathetic and epidural blocks have been used but few controlled studies examine their effects. Aggressive analgesia with epidurals may decrease incidence PHN.

REFERRENCES

1. *Cunningham A, et al: The prevention and management of herpes zoster: MJA: 2008: 188: 3: 171.*
2. *Dworkin R et al: Recommendations for the Managemnet of Herpes Zoster: CID:2007: 44 (Suppl 1): S1*

QUESTION 9 ***NON COMPULSORY***

An East African refugee is referred to your outpatient pain clinic with persisting widespread pain. He reports a history of imprisonment and interrogation. How does this history influence your evaluation?

General background

Epidemiology

- estimated that 5 – 35% of all refugees have suffered torture
- women and children make up for more than 2/3rds of the refugee pop
- women are more likely to suffer sexual torture than men
- practiced systematically in more that 120 countries
- torture has/ is used as a political tool in Zimbabwe, Somalia, Sudan, The Democratic Republic of Congo and Libya

Risk factors for torture

- refugee status
- leader of an opposition political party
- being a relative of someone who was tortured
- imprisonment
- pow
- immigrants from totalitarian or military regimes
- members of minority groups
- history of civil war in country of origin

Comorbidity

- refugees have higher prevalence of comorbidity cf with other migrant groups

  – hep B, TB, intestinal parasites, ptsd, depression and anxiety
- ptsd – 1% in non tortured refugees, 20% in refugees who experienced battlefield conditions and 67% in tortured

Results of torture

- the whole spectrum of pain and psychological disorders can arise out of torture
- penetrating wounds (gunshot, stab), electrocution, repetitive blunt trauma, violent sexual assault, sustained extremes of posture or suspension, amputation and crush injuries are all commonly applied in torture and can result in chronic musculoskeletal , neuropathic or visceral pain, anyone of these can result in widespread pain complaints
- In addition chronic headache, epilepsy and cognitive impairment may result from repetitive blunt head blows
- Torture survivors most commonly experience post traumatic stress disorder and depression

Patients Perception

- in many countries medical staff are collaborators in the torture process, as a result there is often reticence on to attend appointments and adhere to advice / treatment

- patients often feel great shame and embarrassment and haven't ever disclosed torture information

Cultural / language issues

- the stress of migration and adapting to a new culture often amplifies psychological and physical distress

- may not speak english

Conduct of assessment and management

Preparation:

- have access to interpreters, do not use family members

- have access to migrant support agencies and knowledge of ethnic community support groups in your area

- understand that an unaware health worker can easily retraumatise a patient

- have prior knowledge of the political history of a patients prior country, this will help avoid cultural misunderstandings

- as much as possible try to ensure the consulting room doesn't resemble a prison cell i.e. provide adequate lighting, comfortable temperature

- consultation may need to be lengthened

History and examination

- show warmth, respect, understanding and genuine interest

- try not to use repeated closed questions or anything that resembles interrogation

- if examining a member of the opposite sex as much as possible try to have a chaperone present

- inform the patient about the uses of various examination items eg tendon hammer, tunning forks etc

Investigation

- some patients will not tolerate MRI, CT because of prior incarceration in small places

Treatment

- most often will require other professionals especially psychiatrists, psychologists, social worker and cultural liaison officers

- will need detailed explanation of treatment options given cultural, language barriers

REFERENCES

1. *Moreno and Grodin Torture and its neurological sequalae Spinal cord 2002*
2. *Burnett and Peel Asylum seekers and refugees in Britain: The heal of survivors of torture and organized violence 2001 BMJ*
3. *Thomsen, Eriksen, Smidt, Nielsen Chronic pain in torture survivors Forensic Science International 2000*

Instructions to Markers

- a relatively straightforward question requiring some prior thought and planning
- requires a broad response focusing on the various aspects of caring for refuges and survivors of torture

Suggested Marking Scale

Core content	Marks Assigned
General knowledge of epidemiology of pain and torture	1
Knowledge of risk factors of torture	1
Knowledge of comorbidity ie infectious disease And psychological illness	1
Knowledge of various pain and psychological syndromes that can result	1
Demonstrates and understanding of general and specific Issues involved in assessing migrants, refugees and patients Who have experienced torture	1
Understands the need to alter the conduct the consultation And assessment process	1
Bonus content	
Demonstrated a detailed and comprehensive approach to Question	1
Thorough understanding of one aspect of the question Eg pain syndromes, alteration of consultation process, Alteration of treatment process (can be awarded more than once)	1
Detailed understanding of common perceptions of migrants And survivors of torture ie mistrust of medical professionals, Shame and embarrassment of torture process, cultural and Language issues	1
Addition content relevant but not mentioned above	1

QUESTION 10 **_NON COMPULSORY_**

Discuss the concept of "tertiary gain" in relation to persistent pain.

A number of psychosocial factors have been postulated to influence the experience of pain, and it is also considered that psychosocial factors can perpetuate pain complaints and pain behaviour. In such a situation the pain complaints and resultant disability are typically disproportionate to the extent of the objectively demonstrable organic pathology or abnormality.

Among these factors is what has been termed 'tertiary gain'. This term has been used to refer to the concept that someone other than the patient may seek or achieve 'gain' or benefit from the patient's illness.

The phrase 'tertiary gain' was developed by analogy with the concepts of 'primary' and 'secondary' gain. 'Primary gain' is generally considered to be the avoidance of anxiety that might be aroused by conscious awareness of unacceptable affect or conflict; such affects or conflicts are therefore repressed and remain unconscious.

'Secondary gain' is the personal advantage or benefit derived from a symptom or an illness. This might involve avoidance of responsibility, attention, or financial compensation.

'Tertiary gain' might occur where a family member takes on the role of a carer or caregiver, and by doing so avoids involvement in another activity, for example employment that might have been stressful or a cause of job dissatisfaction. For some individuals becoming a caregiver fulfils an altruistic need. Becoming a caregiver might also be financially advantageous (for example, it might create an entitlement to a carer's pension.) In some relationships the partner who becomes a carer achieves dominance over the designated patient, and this dynamic can be considered a 'tertiary gain'.

The tertiary gains available to a 'caregiver' might include:

- gratification of one's altruistic needs,
- financial gain,
- making the ill individual develop dependency on the caregiver, thus elevating the role of the caregiver in that relationship.

Another aspect of tertiary gain involves health care providers, either through 'monetary gain' or by the health care provider's narcissistic need to offer treatment to those who might achieve some degree of improvement while not accepting for treatment patients who are considered 'too difficult'.

The concept of tertiary gain is important when evaluating the patient's social context, both in terms of the family and the social milieu, and also in understanding the patient's role within the health care system.

REFERENCES

1. *Bokan JA, Ries RK, Katon WJ. Tertiary gain and chronic pain. Pain 1981; 10:331-5.*
2. *Dansak DA. On the tertiary gain of illness. Comprehensive Psychiatry 1973; 14:523-34.*
3. *Kwan O, Ferrari R, Friel J. Tertiary gain and disability syndromes. Medical Hypotheses 2001; 57:459-64.*

QUESTION 11 ***NON COMPULSORY***

Why should you advocate the development of an acute pain service at your hospital?

Acute Pain Services (APS) were formalised over 20 years ago and are thought to be current best practice for the care of patients with post-operative and other acute pain conditions.

I would advocate for this service as I am a specialist in Pain Medicine and therefore aware of the potential benefits which include the following: -

1. Better pain control
    - Though the available data is mixed, there is Level III evidence that APS may improve pain relief in the post-operative period using conventional and advanced techniques.
    - Better acute pain control may assist in reducing progression to chronic pain
    - Skilled APS staff to assist with complicated patients such as those with substance abuse history, drug allergies, pre-existing chronic pain and opioid dependence.
    - Skilled APS staff to assist with prescribing adjuvant agents as required such as antihyperalgesics, NMDA receptor blockers, alpha-2 receptor agonists
    - 24 hours / 7 day service for review and advice
    - Improved patient satisfaction
2. Better pain assessment
    - The daily review by the APS results in a regular and detailed assessment.
    - May alert team to surgical complications
    - Early detection of neuropathic pain including CRPS
3. More advanced techniques can be managed on the ward with appropriate education and support. These include
    - Epidural analgesia including patient controlled epidural analgesia
    - IV Opioid PCAs
    - Other regional block techniques
4. Reduced side-effects
    - APS may assist in reducing analgesic induced side-effects (Level III) through regular assessment and treatment as required

5. Education and teaching at multiple levels
    - Ward nursing staff including skills in pain assessment and treatment
    - Medical staff at all levels
    - Training opportunities for anaesthesia and pain medicine trainees
6. Research opportunities
    - Important research opportunities on pain and side-effects. This could be audit or more advanced randomised trials
7. Important developer of guidelines and protocols and assist with the implementation of these through conducting teaching session and ongoing support.
8. Assist with pre-operative planning including patient education
9. Possible improvement in health economics through assisting in fast-track surgery, reduced complication rates, less demand on high dependency beds and shorter hospital stay.

REFERENCES:

1. *Werner MU. The acute pain service: Present and future role. Current Anaesthesia & Critical Care 2007;18:135-139.*
2. *Acute Pain Management:- Scientific Evidence. 2nd Edition. NHMRC. Australia.*

QUESTION 12 ***NON COMPULSORY***

A 71 year old male patient presents with severe metastatic bone pain secondary to prostate cancer. Discuss the evolving pathophysiology of cancer related bone pain and the evidence for novel analgesic therapies.

Bone pain is the most common indicator that prostate cancer has metastasized to the skeleton, with skeletal-related events (SRE's) including pain, anaemia, hypercalcaemia, fractures, spinal cord compression, and decreased mobility contributing to decreased quality of life. At the present time, castration as a preventative therapy in men with hormone sensitive prostate cancer remains an important tool in reducing the incidence of painful bony metastatic disease. In those with hormone-refractory symptomatic bony metastatic disease, radiation therapy and bisphosphonates, together with systemic anti-neoplastic treatments has been the mainstay of treatment. Emerging evidence would also suggest that bisphosphonates may play a preventative role in the development of skeletal metastases, with large prospective clinical trials currently in progress.

In the last decade an increased understanding of the mechanisms by which metastatic prostate cancer produces bone pain and SRE's has occurred with the development of a murine model. This demonstrates concurrent bone destruction and formation and, irrespective of the radiological appearance, with the histological feature characterising all bone metastases being one of increased osteoclastic activity.

Osteoclasts are a multinucleated cell derived from the macrophage/monocyte line. They require the presence of bone marrow stomal cells or osteoblast progeny to secrete macrophage-colony stimulating factor (M-CSF) and receptor for activation of nuclear factor kappa- β ligand (RANK-L) which binds to the receptor for activation of nuclear factor kappa-β (RANK), present on macrophage lines to induce the osteoclast phenotype. Stromal cells and osteoblasts also produce a protein, osteoprotergerin (OPG) which has been shown to inhibit osteoclastogenesis. OPG is a secreted soluble receptor and a member of the tumour necrosis factor receptor family. The quantity of bone resorption is therefore dependent upon the balance between RANK-L, the stimulator of osteoclastogenesis and OPG, its inhibitor and many painful conditions including osteoporosis and inflammatory arthritides such as rheumatoid arthritis result from a shift in this balance. Osteoclasts polarize onto bone and form a "ruffled" membrane which is intimately opposed to the bone matrix. The osteoclast then generates a local acidic extracellular environment (pH 4.0-5.0) at the interface. This is able to mobilise bone mineral whilst a lysosomal protease, cathepsin K subsequently degrades the organic component of bone. The mechanism by which prostate cancer produces increased osteoclastic activity has been identified as stimulation of the receptor activator for nuclear factor kappa β (RANK)-RANK ligand (RANK-L) system. RANK-L binds the RANK receptor on osteoclasts (or their precursors) to induce increased resorptive activity. Denosumab is a human monoclonal antibody which binds to RANK-L neutralizing its activity. Currently in the clinical trial stage, denosumab is being evaluated in a number of non-malignant and malignant (e.g. the treatment of bone loss associated with hormonal ablation in a variety of cancers, treatment of cancer associated bone metastases) bone loss states. The development of OPG analogues which can bind to, and sequester RANK-L, may also provide novel analgesic options for patients with cancer metastatic to bone.

Release of protons by osteoclasts and invading inflammatory cells together with apoptosis produce a local acidosis. This, together with sensory nerve injury (i.e. compression infiltration and destruction) by tumour may contribute to nociception by directly stimulating nociceptors located on the A-δ and C- fibres within the bone. TRPV1 and acid sensing ion channel-3 (ASIC-3) are the two major classes of proton sensing ion channels expressed by these nociceptors. These channels are excited by a decrease in pH with an increase in nociceptive behaviours exhibited in murine models of bone cancer. Administration of TRPV1-receptor antagonists or disruption of the TRPV1 gene results in attenuation of both resting and movement-related nociceptive behaviours. Of particular interest is the fact that antagonists to TRPV1 ion channels have been shown to maintain their efficacy as the tumour progresses. This suggests that TRPV1 continues to be expressed by sensory neurones with tumour growth and that antagonists to this ion channel may be effective in reducing the pain states associated with skeletal metastases.

Sensory and sympathetic nerve fibres richly innervate all parts of the bone marrow, bone matrix and periosteum and as bone remodelling occurs with tumour growth and invasion, so too does sprouting and injury of sensory neurones. With primarily osteoblastic tumours, evidence in murine models suggests that the density of sensory nerve endings within involved marrow is greater than normal. In a sarcoma model of bone cancer both, ongoing and movement evoked pain was associated with a variety of neurochemical and cellular changes occurring both, peripherally and at the level of the ipsilateral dorsal root ganglion (DRG). Gabapentin has been shown in this model to attenuate both ongoing and movement induced nociceptive behaviours. This is not due to modulation of tumour growth, bony destruction or neurochemical chnages at the level of the DRG, but is suggestive of an effect secondary to injury to the primary sensory afferent nerve fibres located in bone.

Neurotrophins are a family of proteins which are important in the development and survival of neuronal sub-populations that express appropriate receptors. Nerve growth factor (NGF) binds a low affinity transmembrane receptor, $p75^{NTR}$ and a high affinity transmembrane receptor trkA. These receptors are located on the terminals of sensory neurones and produce increased sensitivity of nociceptors and a retrograde signal which exerts transcriptional control over the neurone. Pain from metastatic cancer involving bone has been shown to have both inflammatory and specific tumorigenic features. Macrophages and their precursors compose a significant proportion of the tumour mass in tumours metastatic to bone. As these cells express NGF, this would be able to activate or sensitize local sensory nerve fibres which have trk A receptors. As tumour cells proliferate in bone, local sensory fibres are initially distorted, and subsequently injured and destroyed. This results in affected neurones expressing high concentrations of nerve growth factor (NGF) which has been shown to contribute to pain behaviours in mice. NGF has been implicated in the expression and function of a wide variety of substances involved in sensory neurones. These include the neurotransmitters, substance P, BDNF, and CGRP; the receptors, bradykinin and P2X3; the channels, TRPV1, ASIC-3 and sodium channels; the transcription factor ATF-3 and several structural molecules. NGF also modulates the distribution of ion channels and receptors in the sensory neurone as well as altering the supporting cells of the DRG i.e. non-myelinating Schwann cells and macrophage numbers. It would therefore appear that as NGF is intimately involved in the up-regulation, sensitization and disinhibition of neurotransmitters, receptors and channels in the metastatic tumour model that anti-NGF therapies could contribute to analgesia. Anti-NGF therapies are currently in the developmental stages but may offer some hope to those with painful bony metastases.

It has been demonstrated in murine models of prostate cancer metastases, that together with osteoblastic activity and production of newly formed woven bone, albeit without the strength of normal mineralized bone, that there is an extensive array of sensory neuronal sprouting associated with neovascularization. Many of the cells involved in bone metastases have been shown to produce a variety of factors that have previously been described. These either directly excite or sensitize sensory neurones. Prostaglandins produced by the action of COX isoenzymes on cyclo-oxygenase are such substances. Their formation may be inhibited by the non-steroidal anti-inflammatory drugs (NSAIDs), however in patients with cancer their long-term use may be associated with an increased risk of adverse side-effects. COX-2 inhibitors have been shown in an osteolytic model of bone cancer metastases to attenuate behaviours and many of the neurochemical changes suggestive of both peripheral and central sensitization. These agents may also inhibit tumour growth in bone by retarding prostaglandin induced angiogenesis. Reducing tumour growth probably reduces factors produced by tumours that sensitise primary afferent neurones. Like the prostaglandins, endothelins, which are a group of vasoactive peptides, are expressed by prostate cancer and clinical studies have demonstrated correlations between the severity of pain and plasma levels of endothelins in patients with prostate cancer. Endothelins that have been produced by cancer cells have been shown to be important in tumorigenesis by regulating neovascularisation. Hence, endothelin antagonists are likely to assist, not only in management of pain produced by tumours in bone, but also, in tumour growth.

The kinins, and especially bradykinin, have been shown to be released in response to tissue injury. These are known to play a role in both acute and chronic inflammatory pain states via action at two receptors B_1 and B_2. B_1 receptors are expressed at low levels by sensory neurones and are significantly upregulated following tissue injury or inflammation. In prostate cancer metastatic to bone, there is significant bone remodelling with an associated influx of macrophages. Bradykinin has been demonstrated to be released by tumour-associated macrophages. The small to medium sized sensory fibres innervating bone express calcitonin gene-related peptide (CGRP). Many of these have been shown to co-express B_1 receptors, hence, bradykinin released by tumour-associated macrophages activates this population of B_1 receptors contributing to the hyperalgesia and allodynia that is frequently seen in bone cancer. Inhibitors of bradykinin at the B_1 receptor have been shown to attenuate this response in the murine model and therefore provide a further target for the development of novel analgesics.

REFERENCES

1. *Coleman RE. Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity. Clin Cancer Res, 2006: 12(20 Suppl); 6243s-6249s.*
2. *Coleman RE, Guise TA, Lipton A, Roodman GD, Berenson JR, Body JJ, Boyce BF, Calvi LM, Hadji P, McCloskey EV, Saad F, Smith MR, Suva LJ, Taichman RS, Vessella RL, Weilbaecher KN. Advancing treatment for metastatic bone cancer: consensus recommendations from the second Cambridge Conference. Clin Cancer Res, 2008: 14(20); 6387-6395.*
3. *Halvorson KG, Kubota K, Sevcik MA, Lindsay TH, Sotillo JE, Ghilardi JR, Rosol TJ, Boustany L, Shelton DL, Mantyh PW. A blocking antibody to nerve growth factor attenuates skeletal pain induced by prostate tumor cells growing in bone. Cancer Res. 2005: 65(20); 9426-9435.*

4. *Halvorson KG, Sevcik MA, Ghilardi JR, Rosol TJ, Mantyh PW. Similarities and differences in tumor growth, skeletal remodelling and pain in an osteolytic and osteoblastic model of bone cancer. Clin J Pain, 2006: 22(7); 587-600.*
5. *Mercadante S. Malignant Bone Pain: pathophysiology and treatment. Pain, 1997: 69; 1-18.*
6. *Peters CM, Ghilardi JR, Keyser CP, Kubota K, Lindsay TH, Luger NM, Mach DB, Schwei MJ, Sevcik MA, Mantyh PW. Tumor-induced injury of primary afferent sensory nerve-fibres in bone cancer pain. Experimental Neurology, 2005: 193; 85-100.*
7. *Pezet S, McMahon SB. Neurotrophins: Mediators and Modulators of Pain. Annu. Rev. Neurosci. 2006: 29;507-538.*
8. *Sevcik MA, Ghilardi JR, Halvorson KG, Lindsay TH, Kubota K, Mantyh PW. Analgesic efficacy of bradykinin B_1 antagonists in a murine bone cancer pain model. J. Pain, 2005: 6(11); 771-775.*
9. *Sevcik MA, Ghilardi JR, Perters CM, Lindsay TH, Halvorson KG, Jonas BM, Kubota K, Kuskowski MA, Boustany L, Shelton DL, Mantyh PW. Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization. Pain, 2005: 115; 128-141.*
10. *Teitelbaum SL. Bone Resorption by Osteoclasts. Science, 2000: 289; 1504-1508.*

Marking Guide

- acknowledge the issues of bone metastases in men with prostate cancer
- presumed mechanism by which bone metastases produce skeletal-related events
- emerging evidence for prophylactic use of bisphosphonates to attenuate metastatic spread and growth of some tumours in bone
- RANK-RANKL versus osteoprotergerin in the balance of osteoclast activity
- inhibition of RANK-L by the human monoclonal antibody, denosumab (clinical trials)
- direct stimulation of Aδ- and C-nociceptors by acidic environment produced by increased osteoclast activity via TRPV1 and ASIC-3 ion channels on sensory neurones
- increased sensory nerve ingrowth associated with bone remodelling and tumour growth → the potential efficacy of gabapentin/pregabalin in pain secondary to bone metastases
- the role of neurotrophins especially NGF in producing pain behaviours in murine models and hence anti-NGF provides a target for future analgesic development.
- inhibitors of prostaglandins especially the COX-2 NSAIDs may not only attenuate nociception, but may also have a role in reducing tumour burden.
- the kinins and especially bradykinin acting at B_1 receptors. Inhibition of B_1 receptors has been demonstrated to reduce the hyperalgesia and allodynia associated with the mouse model of sarcoma

QUESTION 13 ***NON COMPULSORY***

You are asked to attend a hospital seminar on euthanasia to discuss the chronic pain aspects in a panel discussion. Outline your preparation for this discussion.

<u>Background information on euthanasia / assisted suicide:</u>

- Strong public support in European countries (50-85%) and US (34-65%).
- Lower support among physicians (~40%) and few would be willing to perform euthanasia or physician assisted suicide (PAS).
- Majority have terminal cancer (~80%) with other categories including cardiopulmonary disease, nervous system disease, HIV/AIDS and a small category of elderly patients with nonfatal diseases (e.g pain, osteoporosis). Utilized by all 7 patients in Northern Territory when it was briefly legalized.
- Different and distinguishable from withdrawing life support or providing pain medications even with the increased risk of respiratory depression and death.
- Illegal in most countries including Australia.
- Accounts for only a small proportion of deaths (~2% or less) compared to alleviation of pain and symptoms with opioids with probable life shortening effects (~20-30%) and decisions to forgo treatment (20-30%)

<u>Reasons for patients requesting euthanasia or PAS:</u>

- Physical reasons
    - Pain
    - Loss of control of bodily functions

- Social reasons
    - Need of long term care – being a burden to family and friends

- Pschoexistential reasons
    - Control on circumstances of death (autonomy)
    - Loss of dignity
    - Less able to engage in activities making life enjoyable
    - Hopelessness
    - Depression
    - Distress with suffering

It appears that pain and pain related functional impairment is not a major determinant in use of euthanasia or PAS (only 24% rated as major consideration in Oregon, USA). However, for terminally ill patients, pain was among the factors associated with personally considering euthanasia.

Other issues equally important such as autonomy, fear of deterioration, hopelessness and other psychoexistential issues.

<u>Important values in both proponents of euthanasia and palliative care:</u>

- Reducing human suffering

- Not reducing patients to the biological and neglect of the human patient as a complete person
- Control by patient at the end of life
- Recognition that something other than death itself is the “worst evil” that should be averted and a view that a “good death” is possible.

Important considerations in end-of-life care which constitutes a “good death”:

- Good pain and symptom management
- Treatment preferences honoured with clear decision making / mentally aware
- Preparation for the end of life
    - Attention to spirituality, funeral arrangement planned, not being a burden to family, presence of family.
- Achieving a sense of completion about one’s life
    - Remember accomplishments / life review, being able to help others, resolving unfinished business and saying good-byes.
- “Being treated as a whole person” – including maintaining one’s dignity
- having a trusting relationship with patient’s health care professionals – not just the patient’s disease.

Strategies:

1. Enhanced access to quality multidisciplinary palliative-hospice care, mental health services and pain management.

2. Address patient’s fear of intractable pain and its management.

3. Treat depression and other psychiatric co-morbidities.

4. Implement end-of-life care / palliative care principles to maximize duce suffering (as above).
    - “good death”
    - good pain and symptom control
    - avoid over medicalization with technology at the end of life – treating the person
    - attention to patient preferences, autonomy and control issues
    - preparation for death
    - assist with achieving a sense of completion in patient’s life
    - maintaining trusting relationship with health care professionals

5. Providing knowledge and clarity about the availability of last-resort options for responding to intolerable suffering despite comprehensive caring efforts. This is important to allay patient’s fear of being trapped in a life filled with suffering without the prospect of a timely escape. These measures include:
    - proportionately intensive symptom management
    - stopping or not starting life-sustaining therapy
    - sedation to relieve intractable symptoms
    - voluntary stopping eating and drinking

REFERENCES

1. *Emanuel EJ. Euthanasia and Physician-assisted suicide. A review of the empirical data from the United states. Arch Intern Med 2002; 162: 142-152.*

2. *Hurst SA, Mauron A. The ethics of palliative care and euthanasia: exploring common values. Palliative Medicine 2006; 20: 107-112.*
3. *Van Der Weyden MB. Deaths, dying and euthanasia debate in Australia. MJA 1997; 166: 173.*
4. *Steinhauser K, Christakis N, Clipp E et al. Factors considered imprtant at the end of life by patients, family, physicians and other care providers. JAMA 2000; 284(10): 2476-2482.*
5. *Quill TE. Dying and decision making – evolution of end-of-life options. NEJM 2004; 350 (20): 20292032.*

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QUESTION 14 ***NON COMPULSORY***

You are referred a patient for a procedure to help control chronic pancreatitis related pain. Discuss your approach to this request and justify your position.

Chronic pancreatitis (CP) is a disease process characterised by irreversible morphological changes that typically cause pain and loss of function. Alcohol is a common precipitating cause in the majority of cases. Other causes include tropical pancreatitis, hereditary, gallstones, infective and envenomation. Chronic pain is present in 80-90% of patients. It is usually severe dull deep epigastric pain radiating through to the intrascapular area. It is recurrent, long standing and severe, commonly leading to chronic intake of analgesic medications including strong opioids.

In managing patients with this pain modifying risk factors most notably alcohol intake is of the utmost importance. The mechanism for pain in still poorly understood and treatment is largely empirical. Chronic pain many be either stimulus independent or postprandial pain.

Though medical management of pain is the mainstay of treatment some interventions may merit consideration. It must be highlighted that outcome studies of many of these interventions have not been repeated are of low quality or are a result of small numbers. This must be emphasised to any patient seeking an intervention for the pain associated with CP. Inflammatory cytokines and gene expression similar to those that occur in neuropathic pain also have been identified in CP. This suggests that agents such as tricyclics antidepressants and anticonvulsants may be useful. More recently tramadol in higher doses than normal may be useful.

Any surgical intervention such as decompression of pancreatic ducts and relief of ductal hypertension has merit as has decompression of pancreatic parenchymal tissue analogous to compartment syndrome. This may decrease pressure within the pancreas and tissue acidosis. A surgical opinion from a specialist centre should be sought.

Endoscopic procedures involving stricture dilation, stents and stone extraction have resulted in improvements in approximately 2/3 of patients. Extracorporeal shock wave lithotripsy in addition to endoscopic therapy has some added benefit. These are generally better when dilated ducts and calcification / stones are identified. Surgical options should only be considered if an inflammatory mass is present and resectable or obstruction and dilated ducts are greater than 5-7 mm. Various surgical approaches have been studied. The Whipples or the more conservative Frey procedure found to be most useful.

Neuroslysis or nerve blocks such as celiac plexus blockade or splanchnic blockade shown to be of great use in carcinoma of the head of the pancreas have been disappointing in the long term management of CP. Recent technological advances have allowed an ultrasound guided endoscopic celiac plexus block to be safe repeatable and cost effective when compared to alternative coeliac plexus block approaches. It is more useful in acute exacerbations episodes rather than constant dull aching pain. Coeliac plexus blockage using phenol or alcohol may result in significant disorders of gastrointestinal function and / or orthostatic hypotension and is inadvisable for non cancer pancreatic pain.

Splachnecectomy using videoscopic thoracosopy (VSPL) may be of some longer term benefit. Its utility is more predictable if it is preceded by differential epidural analgesia(DEA). If DEA identifies patients whose pain is primarily visceral VSPL is likely to be more successful.

Acupuncture in any of its techniques and TENS have been shown to be ineffective. Spinal cord stimulation has proved effective in a small series of patients and is a less invasive procedure when compared with surgery should be considered.

When advising a patient with CP on an intervention for pain relief, realistic goals must be identified. Endoscopic decompression duct dilation and stenting carries a low morbidity and might be considered first. VSPL preceded by DEA might then be seen as the next step. Spinal cord stimulation should also be considered prior to major surgery. Any procedure offered must be accompanied by multidisciplinary support and measurement of not only pain reduction using the visual analogue pain score (VAPS) but also functional improvement and quality of life scales.

REFERENCES

1. *Fasanella KE et al*
   Pain in Chronic Pancreatitis and Pancreatic Cancer
   Gastroenterol Clin N Am 36 (2007) 335-364

2. *Bradley EL et al*
   Thoracoscopic Splanchnicectomy for “small duct” chronic pancreatitis: case selection by differential epidural analgesia
   J Gastrointest Surg. 1998 2(1) 88-94

QUESTION 15 ***NON COMPULSORY***

Write brief notes on a recommended set of "core outcome measures" for clinical trials evaluating new analgesic agents for persistent non-cancer pain.

Object of question:

- To determine whether candidate is aware of currently accepted "core outcome measures" for assessing analgesic efficacy in the clinical trials component of drug evaluation for persistent pain (Phases II - IV)(Williams 1988; Dworkin, Turk et al. 2005).

General Comments

- Over recent decades there has been a call to develop an agreed set of outcome measures for the evaluation of pain treatments (Williams 1988).
- No single measure is able to reflect the complex nature of the pain experience. A multidimensional assessment is required considering the biological, psychological, sociocultural and economic aspects of the treatment.
- While recommendations have been made, these are likely to change over time and are a starting point (IMMPACT recommendations - Dworkin, Turk et al. 2005).
- Analgesic interventions *used in isolation* are not likely to result in sustained improvement in physical, psychological and social functioning. Improvements in perceived pain may provide an environment where physical and psychological rehabilitation is more successful. For most people a multidimensional pain treatment program is required.

Qualities of an outcome measure

The most important issue is not which measures are used but how reliable and valid they are. Evaluation of an outcome measurement therefore requires an assessment of:

- Reliability - the consistency, stability and repeatability of an instrument.
- Validity - the appropriateness and usefulness of a particular measurement in making an inference about an individual's behaviour.
- Other factors:

  e.g. difficulties associated with administration of measure (subject and administrator), availability and equivalence of versions for different patient groups and languages.

Several domains have been suggested to be measured routinely (IMMPACT recommendations - Dworkin, Turk et al. 2005)

1. Pain
   - unidimensional (numerical rating scale - NRS 11)
   - use of rescue medication
   - categorical rating (none, mild, moderate, severe) if NRS difficult
2. Physical functioning
   - Multidimensional Pain Inventory Interference Scale OR

- Brief Pain Inventory interference items

3. Emotional functioning
   - Beck Depression Inventory OR
   - Profile of Mood States
4. Participant ratings of global improvement and satisfaction with treatment
   - Patient Global Impression of Change
5. Symptoms and adverse events
6. Participant disposition (Detailed information regarding participant recruitment and progress through the trial)

Other considerations (Williams 1988).

- It is crucial that the type of pain is carefully defined (that an accepted taxonomy is used).
- Economic implications of the treatment should also be assessed.

Outcome measures may also be broadly classified as (Gatchel and Theodore 2008)**:**

Patient reported

- Pain measures - unidimensional pain intensity scales (NRS, VAS, categorical scales) and multidimensional measures (Pain Disability Questionnaire, McGill Pain Questionnaire, Brief Pain Inventory)
- Health related quality of life measures e.g. Medical Outcomes Short Form 36-Item Health Survey (SF-36), EuroQoL etc. Need to indicate the minimally clinically important difference (MCID) for measure used.
- Psychological measures - e.g. depression (Beck Depression Inventory)

Objective

- Return to work (one year and beyond)
- Healthcare utilization

Quantitative measurements are sometimes used in specific circumstances

Direct measurement (quantitative sensory testing):

Subjective quantitative pain rating over area of hypersensitivity to nociceptive stimuli eg thermal, chemical, pressure, ischaemic or electrical stimulation

Indirect or surrogate measurement of pain:

- Supraspinal measurement – cortical evoked responses (e.g contact heat evoked potentials)
- Other measures eg muscle tension, vasodilation, HR and BP – little validation in clinical or laboratory scenarios

Specific measures may be required for differing pain types and patient groups.

- *Pain types e.g.* Neuropathic pain (Neuropathic Pain Scale (NPS), Leeds assessment of neuropathic pain symptoms and signs (LANSS). Neuropathic Pain Questionnaire (NPQ), Neuropathic Pain Symptom Inventory (NPSI), etc).
- *Children and neonates* e.g. Neonatal Pain Scale, Faces Scale etc
- *Patients with cognitive impairment* e.g. Discomfort Scale for Dementia of Alzhiemers types (DS – DAT)
- *Non communicative adults* (cognitive or communication impairment) e.g. Behavioural Pain Rating Scale, Behaviour Pain Scale, Critical Care Observation Tool, Non Verbal Pain Scale
- *Senior Citizens* e.g. Geriatric Pain Measure
- *Aboriginals and Torres Strait Islanders* - no tools yet developed

Closing comment

While consensus remains difficult in specific patient populations, the collection of comparable outcome measures remains crucial for the advancement of evidence based practice in Pain Medicine. For treatments aimed at persistent pain consideration must be given to the measurement of long term outcomes (> one year).

REFERENCES

1. *Dworkin, R. H., D. C. Turk, et al. (2005). "Core outcome measures for chronic pain clinical trials: IMMPACT recommendations." Pain **113**: 9-19.*
2. *Gatchel, R. J. and B. R. Theodore (2008). "Evidence-Based Outcomes in Pain Research and Clinical Practice." Pain Practice **8**(6): 452-460.*
3. *Williams, R. C. (1988). "Toward a set of reliable and valid measures for chronic pain assessment and outcome research." Pain **35**(3): 239-251.*

Suggested Marking

This is a difficult question requiring a very broad approach with evidence of prior thought and planning. Uniform abbreviations should be acceptable eg VAS, SF – 36, MRI, PET.

General comments (2)

- Multiple measures have been developed (1)
- Consensus recommendations have been made i.e. IMMPACT (1)

Domains requiring measurement (2)

- Pain + physical functioning + emotional functioning (1)
- Participant ratings of global improvement and satisfaction with treatment + symptoms and adverse events +/- Participant disposition (1)

Qualities of an outcome measure (2)

- Reliability & validity (1)
- e.g. difficulties associated with administration of measure, available in different languages etc (1)

Specific examples of outcome measures (2)

- Pain intensity + physical function + emotional function (1)
- Comments regarding special groups (1)

Overall impression (2)

Total marks: 10

Alternative marking suggestions

Core content (one mark each - 5)

1. Multidimensional nature of pain requiring assessment of numerous domains
2. The lack of uniformity in the use of outcome measures in clinical and laboratory setting, need for consensus (e.g. IMMPACT)
3. Comprehensive categorisation of clinical data used in outcome measurement e.g. pain specific, physical function, emotional function, patient assessment of treatment, side effects, participant disposition & economic impact
4. Understanding of the requirement for different outcome rating scales in different clinical scenarios eg children, elderly, cognitively impaired, arthritis, neuropathic pain
5. details of use of outcome measurement

Bonus content (one mark each - 4)

6. understanding regarding important properties of measures especially reliability and validity
7. detailed categories of outcome measures with examples eg FIM, SF–36
8. detailed understanding on commonly used outcome measures eg McGill, Brief Pain Inventory, VAS etc
9. additional content e.g. sensible comments on limitations of various outcome measurements

Global impression (one mark - 1)

Total mark = 10 (5 + 4 + 1)