Management of difficult pain and other symptoms in palliative care
Epidemiology of pain in End of Life care

• Prevalence
  – 35-96% in 19 trials involving 10,379 patients with cancer
  – 63-80% in 3 trials of 942 patients with AIDS
  – 41-77% in 4 trials of 882 patients with heart disease
  – 34-77% in 3 trials of 372 patients with COPD
  – 47%-50% in 2 trials of 370 patients with renal disease
The level of need for palliative care: a systematic review of the literature, PJ Franks et al, Palliative Medicine 2000

Table 4  Prevalence of symptoms in patients with cancer and noncancer terminal disease (%)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Patient</th>
<th>Pain</th>
<th>Dyspnoea</th>
<th>Fatigue</th>
<th>Vomiting</th>
<th>Nausea</th>
<th>Poor Sleep</th>
<th>Weakness</th>
<th>Confusion</th>
<th>Appetite</th>
<th>Incontinence</th>
<th>Constipation</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Mixed (n = 262)</td>
<td>52</td>
<td>42</td>
<td>–</td>
<td>20</td>
<td>16</td>
<td>19</td>
<td>52</td>
<td>23</td>
<td>–</td>
<td>35</td>
<td>24</td>
<td>18</td>
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<tr>
<td>24</td>
<td>Mixed (n = 846)</td>
<td>60</td>
<td>20</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>35</td>
<td>5</td>
<td>–</td>
<td>25</td>
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<tr>
<td>25</td>
<td>Mixed (n = 53)</td>
<td>66</td>
<td>62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>81</td>
<td>38</td>
<td>66</td>
<td>42</td>
<td>51</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>26</td>
<td>Mixed (n = 26)</td>
<td>69</td>
<td>69</td>
<td>88</td>
<td>27</td>
<td>54</td>
<td>88</td>
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<tr>
<td>7</td>
<td>Random (n = 471)</td>
<td>67</td>
<td>49</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>36</td>
<td>38</td>
<td>–</td>
<td>38</td>
<td>32</td>
<td>33</td>
<td>–</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Disease-specific studies</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>27</td>
<td>HIV (n = 40)</td>
<td>–</td>
<td>–</td>
<td>57</td>
<td>–</td>
<td>–</td>
<td>65</td>
<td>–</td>
<td>–</td>
<td>63</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>28</td>
<td>Motor neurone disease (n = 22)</td>
<td>–</td>
<td>–</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>64</td>
<td>100</td>
<td>–</td>
<td>86</td>
<td>18</td>
<td>32</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>29</td>
<td>Coronary heart disease (n = 600)</td>
<td>63</td>
<td>51</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>45</td>
<td>–</td>
<td>43</td>
<td>37</td>
<td>30</td>
<td>59</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>30</td>
<td>Dementia (n = 170)</td>
<td>64</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>83</td>
<td>57</td>
<td>59</td>
<td>72</td>
<td>–</td>
<td>61</td>
<td>–</td>
</tr>
</tbody>
</table>
All patients suffered from at least one symptom frequently and almost constantly with an average of 6 symptoms.

*Oechsle 2014 JPSM*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency, Mean (SD)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>2.43 (1.55)</td>
<td>75%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1.56 (1.61)</td>
<td>89%</td>
</tr>
<tr>
<td>Tiredness</td>
<td>2.85 (1.26)</td>
<td>95%</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>3.20 (1.09)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.67 (1.54)</td>
<td></td>
</tr>
<tr>
<td>Thirst</td>
<td>1.43 (1.52)</td>
<td>82%</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>2.52 (1.53)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.80 (1.40)</td>
<td>79%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.34 (1.52)</td>
<td></td>
</tr>
<tr>
<td>Problems with urination</td>
<td>1.08 (1.42)</td>
<td></td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>1.77 (1.58)</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>0.87 (1.25)</td>
<td>36%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.15 (1.43)</td>
<td>46%</td>
</tr>
<tr>
<td>Sadness</td>
<td>1.43 (1.57)</td>
<td>49%</td>
</tr>
</tbody>
</table>
Findings: Oechsle 2014 JPSM

• Perceived sense of dignity was strongly associated with symptom burden
  – The intensity of symptoms (highest)
  – Symptom distress
  – Frequency of symptoms
  – Perceived treatment requirements

• Symptoms with psychological symptoms especially anxiety and sadness
  – Highest correlations with symptom distress, existential distress, peace of mind and social support

• Perceived sense of dignity and psychological well being are closely related
Good Symptom Control

Multidimensional Picture

- Physical
- Psychological
- Functional
- Social / financial
- Spiritual
Assessment in patients with advanced disease

• Assessment
  – Continuous
  – Changing situation
  – Even close to death

• Take a good history
• If not able to
  – non verbal cues
  – Information from family
  – nurses and other staff
Clinical Examination

- Crucial
- Important clues if no verbal communication possible with the patient
- Can be non intrusive
- Communicate reason why
- Get assistance from other staff or family
- With a caring and respectful attitude
- Examine the whole person including mouth/skin/ bladder/bowel
Investigations

• Perform investigations that add information to decision making or to symptom control
• Do not do investigations if you are not going to act on them
• Consider the burden of the investigation on the family
  – Travel
  – Cost
  – Symptoms during procedure
Principles of symptom control

• Assessment
• Diagnose the cause of the symptom
• Is there a reversible cause
  – Can it be treated easily
  – Is the treatment appropriate or futile
• Treat reversible conditions
• Manage the symptom
  – Are there non-pharmacological management
  – Pharmacological management
• Communication with patient / family / staff
• Education of patient / family / staff
Pain management

• Assessment
• Diagnose the cause
• Treatment with multi-modality treatments
• Understanding opioids (morphine) and their side effects
• Identifying neuropathic pain
• Using adjuvant medications
• Psychological aspects to pain management
Neuropathic pain

• Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as
• “pain initiated or caused by a primary lesion or dysfunction of the nervous system” (Merskey and Bogduk 1994)
• “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” Treede 2008
Chronic and Neuropathic Pain

• Chronic Pain:
  – *pain on a long-term basis, with no apparent tissue injury component*
  – *e.g.: complex regional pain syndrome, back pain, cervical pain etc.*

• Neuropathic Pain:
  – *large number of pain syndromes*
  – *aberrant somatosensory processes*
  – *lesion in the peripheral or central nervous system*
  – *e.g.: peripheral neuropathies, PHN, malignant infiltration*
  – *burning, shooting, electric, stabbing*
**The Pathway of Pain**

1. Painful stimulus
2. Release of prostaglandins
3. Stimulation of nociceptors
4. Impulse enters CNS via dorsal horn
5. Impulse ascends spinothalamic tract
6. Processing in mid brain
7. Interpretation in cerebral cortex

**The Natural Modulation of Pain**

- Endorphins
- Serotonin and noradrenaline reuptake inhibition activates descending pathways

**The Therapeutic Modulation of Pain**

- Tricyclic antidepressants
- Opioids
- Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates
Pain descriptors
A: continuous dysaesthesias
B: Lancinating (stabbing) dysaesthesias
Causes of Neuropathic pain in Cancer

- Direct invasion by tumour
  - Plexopathies, cord compression, peripheral nerve compression
- Chemotherapy agents
- Immune modulators
- Radiotherapy – fibrosis (late complication)
- Herpes Zoster
- Other benign diseases: Diabetes, degenerative spine disease
- Paraneoplastic syndrome
Do opioids have a role?

- Neuropathic pain can respond to opioids
- Different efficacy
- Reliance on adjuvants or anti-neuropathic measures
Pain states

• In Chronic pain states and neuropathic pain
  – Down-regulation of opioid receptors and therefore opioids may not have as much effect
  – Central sensitisation is a significant cause for these pain states

• Bone pain
  – Neuropathic element to the pain state
Non-opioid analgesia

• Neuropathic pain
  – Antidepressants: amitriptylline, SSRI’s
  – Anticonvulsants: sodium valproate, tegretol
• Gabapentin (neurontin)
• Pregabalin (lyrica)
• NMDA antagonists
  – E.g. Ketamine
• Establishment of the role of biphosphonates
  – Breast and prostate cancer, multiple myeloma
  – Other solid tumours?
Antidepressants

• Analgesic efficacy in chronic pain / neuropathic pain
• Block reuptake of monoamines
• McQuay systematic review 1996
  – 30/100 will get >50% pain relief
  – NNT 3 in DN, adverse events 2.8
• Studies in non-malignant pain
  – Diabetic neuropathy / PHN
• Significant SE
• Dosing
• Response within 24-72 hours
Antidepressants

• Tricyclic antidepressants
  – Amitriptyline
  – Doxepin, imipramine, desipramine, nortriptylline

• Selective serotonin reuptake inhibitors
  – Paroxetine
  – Citalopram

• Monoamine oxidase inhibitors
  – Phenelzine
Anticonvulsants

• Suppresses paroxysmal discharges of pain fibers
• Reduces neuronal hyperexcitability
• DN: NNT 2.5 for effectiveness, 3.1 Adv E, 20 serious adv e McQuay 1995
• Studied in Phenytoin, Carbamazepine, sodium valproate
• Mainly studied in CNMP, but also cancer
Anticonvulsants

- Sodium Valproate
  - 100 – 200 mg nocte to bd and then titrate to 800-1,000mg / day
  - RR cancer 55.6%
- Carbamazepine 100 mg nocte
- Clonazepan useful in the terminal setting
  - 1-2mg/day
- Response within a week
- SE: sedation, dizziness, nausea, unsteadiness, hepatic toxicity
Gabapentin

- designed as an analogue of GABA
- site unknown, mechanism unknown (Ca channel)
- PHN, complex regional pain syndrome, peripheral neuropathies
- Prevent allodynia and hyperalgesia
- Acts also on NMDA receptors

- ???opioid sparing effect
- Improved pain and sleep
- Dose 1.5g to 3g to have efficacy
- Drowsiness, dizziness, ataxia, peripheral oedema
- Lomotigine (not promising)
Pregabalin (Lyrica)

- Analogue of GABA
- Analgesic and anticonvulsant activity
- PHN main studies showing efficacy
- Indication: Rx of neuropathic pain in adults
- SE: dizziness, somnolence
- Dose adjustment in renal impairment
- Dose: 150 to 600mg / day in 2 divided doses
NNT’S FOR PERIPHERAL NEUROPATHIC PAIN STATES

- Carbamazepine 2.3 (CI 1.6 - 3.8)
- Sodium Valproate 2.3
- Amitriptyline 2.4 (CI 2.4 – 4.0)
- Gabapentin 3.8 (CI 3.5 - 5.7)
- Pregabalin 4.2 (CI 3.9 – 6.6)
- Tramadol 3.9 (CI 2.7 - 6.3)
- Lamotrigine 4.0 (CI 2.1 - 4.2)
- Topiramate 7.4 (CI 4.3 – 28.5)
Side effects

• Ineffective assessment and treatment of side effects
• Adjuvants: interactions
• NSAID’s GIT / renal side effects
• If well controlled, can titrate opioids well
• Titrate adjuvants separately
• Opioid substitution
‘Wind Up’

• Prolonged response to a noxious stimulus (dramatic increase in duration and magnitude of cell responses, but input into the spinal cord remains the same)

• Activation of:
  – neurotransmitters (glutamate, substance P, NO)
  – receptors (NMDA)
  – inflammation and chemicals (neurotropin)
  – genes (Cfos)
NMDA Antagonists

• NMDA receptor leads to functional alteration in central transmission process; hyperalgesia and allodynia

• Ketamine:
  – dissociative anaesthetic
  – analgesia, slight respiratory depression, CV stimulation
  – restores the response to morphine
  – SE: amnesia, sedation, emergence phenomena (benzodiazepines)
Ketamine

• Chronic Non-malignant pain
  – post-herpetic neuralgia
  – phantom limb pain
  – peripheral neuropathy

• Cancer Pain
  – combined use with opioids
  – intractable neuropathic pain, tenesmus, spinal cord compression etc.

• Parenteral versus oral Ketamine
Ketamine study

• Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain (*Jnl Clinical Onc* 2012)

  • Janet Hardy, Stephen Quinn, Belinda Fazekas, John Plummer, Simon Eckermann, Meera Agar, Odette Spruyt, Debra Rowett, and David C. Currow

• 185 participants were included in the primary analysis

• There was no significant difference between the proportion of positive outcomes (0.04; 95% CI, 0.10 to 0.18; P .55) in the placebo and intervention arms (response rates, 27% [25 of 92] and 31% [29 of 93])

• There was almost twice the incidence of adverse events worse than baseline in the ketamine group after day 1 (incidence rate ratio, 1.95; 95% CI, 1.46 to 2.61; P .001) and throughout the study

• Those receiving ketamine were more likely to experience a more severe grade of adverse event per day (odds ratio, 1.09; 95% CI, 1.00 to 1.18; P .039).
Methadone

• Research underway looking at Methadone activity on NMDA receptors
  – analgesia
  – NMDA antagonist

• Limitation by long and unpredictable half life, dosing schedule and available preparations

• Adjuvant role in cancer pain for resistant neuropathic and wind-up pain
Methadone

- Can be used an opioid substitution if toxicity from Morphine
  - Need to use opioid equianalgesic tables to decide on the dose
- Can be added to other opioid if there is significant neuropathic or ‘wind up’ pain not responding to other anti-neuropathics
Anaesthetic agents

• Block Na channels and aberrant electrical activity or hypersensitivity

• Oral
  – Mexiletine (150mg bd), flecainide
  – Poor efficacy in practice and SE

• Topical local anaesthetics

• Parenteral lignocaine infusion
  – Bolus or continuous
  – IV, S/c
Pain interventions

• TENS

• Massage, acupuncture

• Regional blocks and neurolytic blocks
  – Coeliac plexus, intercostal, trigger points

• Spinal analgesia (opioids and anaesthetics)
  – Epidural catheter, Intra-thecal

• Surgical procedures
Table 3. Australian Pain Society evidence-based recommendations for the pharmacologic management of neuropathic pain.

- Noradrenergic antidepressants nortryptiline, desipramine, amitriptyline, venlafaxine, duloxetine
- Calcium channel alpha 2-delta ligands gabapentin, pregabalin
- Lignocaine, topical lignocaine
- Opioid agonist morphine, oxycodone, methadone
- Partial Opioid-agonist tramadol
Initiate symptom treatment with one or more of the following:

- A secondary-amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
- A calcium channel a2-d ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP, topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies
- Evaluate patient for nonpharmacological treatments and initiate if appropriate
Eight studies were eligible (five randomized controlled trials) that recruited 465 patients in total, of whom 370 (79.5%) completed the study period.

A narrative analysis was performed because clinical and methodological heterogeneity prevented metanalysis.

Included studies suggested that adjuvants improve pain control within 4–8 days when added to opioids for cancer pain.

The strongest evidence supports gabapentin.

An increase in adverse events is likely.

For all adjuvants, the effect size was much less than that seen in patients with non-cancer neuropathic pain.

• 120 cancer patients with neuropathic pain
• In all 4 groups there was a reduction in VAS over the 4 weeks at each visit but PG had the most reduction at Wk 3 and Wk 4
• PG had higher reduction of burning, lancinating pain and dysesthesia
• All had morphine sparing effects especially with PG
References

- Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. 

- Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain. Janet Hardy et al JLN Clin Onc 2012
DYSPNOEA

• Diagnose and TREAT THE CAUSE
  • Infection
  • Broncho-constriction
  • Tumour progression
• Positioning and breathing techniques
• Air flow
• Oxygen (continuous or intermittent if helpful)
• Opioids: Morphine
Opioids

- Morphine
- Opioid naïve
  - 2mg (4 to 6 times a day) oral and titrate up
- If already on Opioids
  - 30% increase in their opioid dose
- Pulse doses appear better than slow release opioids
- Breakthrough doses for acute breathlessness or prior to activity
- Timing of doses
DYSPNOEA cont’d

- Treat anxiety
- Supportive care
- Anxiolytics (benzodiazepines may be useful if anxious / panic attacks)
- Meditation / relaxation
- Reassurance and explanation
- Education
  - Patient
  - Family / carer
Nausea and vomiting

- Mr Z
- Metastatic colorectal cancer
- Colostomy / third line chemo stopped
- Initial nausea and now developing vomiting
- Opening bowels every few days
Managing nausea and vomiting

• Assessment
  – History
  – Examination (including rectal exam)

• Investigations
  – AXR erect and supine
  – CT scan with contrast
  – Barium or Gastrograffin enema

• Cause
  – Constipation
  – Bowel obstruction
  – Gastric squash from liver metastasis
Management of Nausea and Vomiting

• GIT cause for nausea and vomiting
  – Metoclopromide 10 mg parenteral (subcutaneous) 3-4 times a day
  – Can increase to 80mg/24hrs
  – Eventually oral if tolerating oral diet

• If ‘central’ cause with predominant nausea
  – Haloperidol 0.5 – 1mg s/c is possible
  – Up to 3mg / 24 hours
  – Eventually oral

• Buscopan (Hysoscine Butylbromide)
  – If bowel obstruction with severe colic
  – But will slow the bowel down
• Bowel management
  – Laxatives softener or propulsive
• Pain
  – Opioids
  – Parenteral if nausea and vomiting
• Psychosocial care
  – Goals and priorities
  – Support
  – Grief counseling
Terminal Care
If three or more of the following symptoms are present it is likely the patient is entering the terminal phase.

- Experiencing rapid day to day deterioration that is not reversible
- Requiring more frequent interventions
- Becoming semi-conscious, with lapses into unconsciousness
- Refusing or unable to take food, fluids or oral medicines
- Irreversible weight loss
- An acute event has occurred, requiring revision of treatment goals
- Profound weakness
- Changes in breathing patterns
What to do

• Recognise dying
• Stop futile treatments that will not improve the patient’s quality of life
• Increase support and comfort for patient
• Good symptom control
• Active and pre-emptive communication with family
Principles of good symptom control

• Understand the patient's trajectory of illness
• Make a good assessment
• Use appropriate investigations if needed
• Communicate the cause for the symptom and the management
• Manage the symptom well
  – Simple but effective treatments
  – Manage side effects for the treatments that you commence
• Use your team to provide holistic care
• Re-assess and continue communication
Medications

• Availability of drugs for symptom control
  – Morphine (oral and parenteral), other opioids
    • Used for pain and breathlessness
  – Metoclopramide / haloperidol for nausea and vomiting
  – Laxatives
    – Haloperidol / Benzodiazepines may be used for agitation and restlessness at the end of life

• Most patients can be managed with oral medications
• Subcutaneous route is better than IV in palliative care especially in the terminal setting
• Subcutaneous route can be used at home
• Know the pharmacology of the drugs
• Able to use these drugs and manage the side effects
Questions?