AGENDA

• Literature Review
• Review of Standards
• General Principles / Guidelines
• Recommendations
• Discussion
NEUROPATHIC PAIN IN CANCER
LITERATURE REVIEW
QUESTIONS ASKED

1. What is the Definition and How do you diagnose NP?
2. What are the existing guidelines for the treatment of cancer NP?
3. Do Opioids have a role?
   – Are any particular opioids better than another?
4. What is the evidence for the use of the following agents in cancer related neuropathic pain?
   – Anti-depressants / Anticonvulsants / Other Adjuvants e.g. Steroids, clonazepam, capsaicin / lidocaine / tapentadol / other?
5. What is the evidence for non-pharmacological approaches to managing neuropathic pain?
   – e.g. TENS, acupuncture, hydrotherapy, psychological interventions?
DEFINITION AND DIAGNOSIS

WHAT IS THE DEFINITION AND HOW DO YOU DIAGNOSE NP?
• Neuropathic pain has is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”
• There is no gold standard test used for the diagnosis of neuropathic pain
• Diagnosis is usually made from clinical history and examination finding
• Screening tools for example McGill Pain Questionnaire, S-LANSS, Neuropathic Pain Questionnaire have not been validated for the diagnosis of cancer related neuropathic pain

References
An international survey of cancer pain characteristics and syndromes. Author(s) Caraceni A., Portenoy R.K. Citation: Pain, September 1999, vol./is. 82/3(263-274), 0304-3959 (01 Sep 1999)
Neupsig criteria in neuropathic cancer pain (NCP). Author(s) Rayment C.S., Kurita G.P., Sjogren P., Bennett M.I. Citation: Palliative Medicine, June 2012, vol./is. 26/4(422), 0269-2163
Pharmacological approaches

What is the evidence for the use of the following agents in cancer related neuropathic pain?

- Opioids / Anti-depressants / Anticonvulsants / Other Adjuvants e.g
- Steroids, clonazepam, capsaicin / lidocaine / tapentadol / other?
IS THERE ANY EVIDENCE FOR THE USE OF OPIOIDS IN CANCER RELATED NEUROPATHIC PAIN?

DR ESRAA SULAIVANY
DR GRAHAM LENG
RECOMMENDATION

• There is evidence to support the use of opioids (tramadol, morphine, oxycodone) in neuropathic cancer pain either as monotherapy or in combination with adjuvant analgesics (Grade B)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbaiza 2007</td>
<td>RCT / N = 36</td>
<td></td>
<td>Tramadol vs placebo</td>
<td>Improvement in pain, less adjuvant analgesia, improved performance status, ADLs, sleep quality</td>
</tr>
<tr>
<td>Patarica-Huber 2011</td>
<td>RCT / N = 75</td>
<td></td>
<td>Gabapentin vs G + Diclofenac vs G + D + Morphine</td>
<td>Pain improved in all groups but best in group 3</td>
</tr>
<tr>
<td>Keskinbora 2007</td>
<td>RCT / Cohort N = 75</td>
<td></td>
<td>Morphine vs Morphine + Gabapentin</td>
<td>Both groups improved</td>
</tr>
<tr>
<td>Li 2010</td>
<td>RCT / Cohort N = 63</td>
<td></td>
<td>Oxycodone vs Oxycodone + Gabapentin</td>
<td>Both groups improved</td>
</tr>
</tbody>
</table>
IS ANY OPIOID SUPERIOR TO ANOTHER?

• There are no trials comparing opioids in cancer related neuropathic pain
# TABLE SUMMARY OF LEVEL 1 TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Treatment Combinations</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Mishra 2012      | RCT / N=120  | Placebo vs Amitriptyline vs GBP vs PG | All drugs have morphine sparing effects  
Pregablin greatest effect clinically |
| Garassino 2013   | RCT / N=75   | Oxycodone + ↑ PG vs ↑ Oxycodone +PG | Control can be achieved with ↑ PG without ↑ opioid dose                   |
| Arai 2010        | RCT / N=52   | GBP 200bd vs GBP 400bd vs Imipramine vs GBP 200bd + Imipramine | Low dose Imipramine significantly ↓ total pain score and daily paroxysmal pain episodes |
| Kesinbora 2007   | RCT / N=63   | ↑ Morphine vs Morphine + GBP | GBP ↑ pain relief                                                        |
| Caraceni 2004    | RCT / N=121  | Opioid + Placebo vs Opioid + GBP | GBP improved analgesia in patients already on opioids                    |
| Mercadante 2013  | RCT / N=48   | Morphine vs Morphine + PG | No difference 2 groups                                                   |
EVIDENCE FOR THE USE OF ANTIDEPRESSANTS FOR THE MANAGEMENT OF CANCER RELATED NEUROPATHIC PAIN

STEVEN SIMPSON
IN CANCER RELATED NP

• Some evidence for TCA (Grade A)
  – RCT Level 1++

• None for Duloxetine
  – A case series in 2012 was inconclusive
IS THERE ANY EVIDENCE FOR THE USE OF STEROIDS IN CANCER NEUROPATHIC PAIN MANAGEMENT?

DR ESRAA SULAIVANY
ROLE OF STEROIDS

• ‘Corticosteroids may have a moderate analgesic effect in cancer patients but the evidence was graded as “very low”’
  – Do Corticosteroids provide analgesic effects in cancer pain? A systematic review Paulsen et al
• The lack of RCTs means that the evidence is very weak.

(Grade C)
IS THERE ANY EVIDENCE FOR THE USE OF CLONAZEPAM IN NEUROPATHIC CANCER PAIN?

DR ESRAA SULAIVANY
CONCLUSION

• There is weak evidence for the use of clonazepam in cancer related neuropathic pain (Grade D)

• Clonazepam as an adjuvant analgesic in patients with cancer related neuropathic pain
THERE IS NO EVIDENCE FOR THE FOLLOWING IN CANCER RELATED NP…

- Paracetamol
- Lidocaine (Topical / IV)
- Capsaicin (Topical)
- Tapentadol
Non-Pharmacological Approaches

What is the evidence for non-pharmacological approaches to managing neuropathic pain?

e.g. TENS, acupuncture, hydrotherapy, psychological interventions?
Acupuncture for Neuropathic pain
COCHRANE REVIEW

• 3 RCTs (total 204 patients)
• One positive high quality study using auriculo-acupuncture
• Two lower quality studies also positive
• Conclusion – ‘There is insufficient evidence to judge whether acupuncture is effective in treating cancer pain in adults’

THERE IS NO EVIDENCE FOR THE FOLLOWING IN CANCER RELATED NP...

- TENS
- Scrambler
- Hydrotherapy
- Psychological Interventions
  - "Although these interventions have not been systematically studied in cancer patients specifically for the treatment of neuropathic pain, recent work in other patient populations experiencing chronic pain suggests their promise"
Current Pre-Existing Guidelines

What are the existing guidelines for the treatment of cancer NP?
EVERYONE SAYS … ‘TREAT WITH AN ANTIDEPRESSANT OR ANTICONVULSANT’

- Treat with Non-Opioid and Opioid medication
  - ESMO, SEOM
- Antidepressant or Anticonvulsant (IA)
  - ESMO, SEOM, NCCN
- XRT to bone mets (II,B)
  - ESMO
- Intraspinal techniques (II,B)
  - ESMO
- Coeliac Plexus Block in pancreatic cancer (II,B)
  - ESMO
- XRT if nerve compression
  - SEOM
- Steroids in Nerve Compression
  - NCCN, SEOM
- Topical Agents (Lidocaine, NSAID)
  - NCCN (IIA)
A WORD ABOUT NICE NOV 2013

- Designed for non-specialists
- For all types of pain including chronic non cancer pain
- Its pharmacological management
RECOMMENDATIONS
‘WHAT’S NICE ABOUT NICE!’

All neuropathic pain (except trigeminal neuralgia)
• Offer a choice of amitriptyline, duloxetine, gabapentin or pregablin as initial treatment for neuropathic pain (except trigeminal neuralgia)
• If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.
• Consider tramadol only if acute rescue therapy is needed.
• Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Treatments that should not be used
• Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:
  – cannabis sativa extract / capsaicin patch / Lacosamide / Lamotrigine / Levetiracetam / Morphine / Oxcarbazepine / Topiramate / tramadol (this is referring to long-term use; see recommendation 1.1.10 for short-term use) / venlafaxine.
REVIEW OF CURRENT STANDARDS
STANDARDS

• All patients with neuropathic pain should be monitored with a pain diary.

• Patients with poorly controlled neuropathic pain should have at least weekly follow-up if an outpatient, and 48 hourly reassessment if an in-patient.

• If neuropathic pain is escalating, an Anaesthetic Pain Specialist should be contacted for advice within 48 hours.
RECOMMENDATIONS
General principles

- Neuropathic pain may be relieved in the majority of patients by multimodal management.
- A careful history and examination are essential. Investigations such as CT and MRI may be appropriate.
- It is important to have a logical and rational approach to prescribing.
- Chemotherapy or radiotherapy may be indicated if the tumour is chemosensitive or radiosensitive.
- Non-pharmacological approaches should be considered including TENS, acupuncture, hydrotherapy and psychological interventions.
- Interventional techniques may be indicated and should always be discussed at an early stage with the Anaesthetic Pain Specialist.
• Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of:
  – Pain control
  – Impact on lifestyle, daily activities (including sleep disturbance) and participation
  – Physical and psychological wellbeing
  – Adverse affects
  – Continued need for treatment

• Consider referring to a specialist pain service and/or a condition-specific at any stage, including at initial presentation and at the regular clinical reviews if:
  – They have severe pain OR
  – Their pain significantly limits their lifestyle, daily activities (including sleep disturbance) and participation
    • (ref NICE guidelines)
Guidelines

• The WHO analgesic ladder should be followed (level 2)
• Strong opioids should be titrated against response. Adjuvants and non-opioids should be used as appropriate (level 1)
• The endpoint of titration is pain relief or intolerable side effects. If dose limiting side effects occur despite the use of adjuvants or other interventions, a switch of opioid should be considered (level 3)
• Figure 28.1 features a flow diagram which may be a useful guide for adjuvant prescribing in neuropathic pain (level 1+)
• If nerve compression is suspected, a trial of corticosteroids could be considered (level 2+) but the evidence is weak e.g. dexamethasone 8mg for 5 days (level 1). Pain relief following the use of corticosteroids often predicts a favourable response to radiotherapy
• Anaesthetic techniques may be indicated. They should always be discussed early with an Anaesthetic Pain Specialist whilst the patient remains fit enough to tolerate any appropriate procedure (see Guidelines on Interventional Pain techniques) (Level 3)

• If the pain is escalating despite the use of recommended guidelines, or if urgent control is required, consider early referral for an Anaesthetic Pain Specialist opinion (level 4)

• For anaesthetic approaches see MCCN Guidelines on Interventional Pain Techniques

• Topical treatment with capsaicin cream may be of benefit in patients intolerant of other treatments (level 1)

• In patients with symptoms that are difficult to control or who have severe aldynia / hyperalgesia, consider admission to a specialist centre (level 4)
Guidelines (cont)

- Methadone is a potent mu agonist and acts as a non-competitive antagonist at the NMDA receptor. It has also been shown to inhibit the re-uptake of serotonin and noradrenaline. Morphine, hydromorphone, fentanyl and oxycodone do not exhibit this additional action. Methadone is therefore often used as a broad-spectrum opioid in the treatment of resistant cancer-related neuropathic pain, where there have been dose-limiting side effects and rapid development of tolerance to the previous opioid. Methadone should only be initiated in a specialist unit (see Guidelines on use of Methadone) (level 1).

- Ketamine may be given as an infusion prior to conversion to an oral preparation where appropriate. It should only be initiated under specialist supervision. It can be given IV (level 1) or SC. Various regimens have been described and the choice will depend on the preference of the specialist team (level 3).

- For treatment of resistant cancer-related neuropathic pain Methadone and or Ketamine could be considered in a specialist palliative setting (see MCCN Guidelines for Methadone and Ketamine use).
Anaesthetic approaches (see Guidelines on Interventional Pain Techniques)

• If the pain is escalating despite the use of recommended guidelines, or if urgent control is required, consider early referral for an Anaesthetic Pain Specialist opinion (level 4) (MOVED into Guidelines)

• The use of peripheral nerve blocks using local anaesthetic and/or corticosteroids may be effective for the relief of pain in the distribution of one or more peripheral nerves (level 3)

• Neurolytic procedures such as a saddle block using phenol may relieve some painful sacral neuropathies. However this may cause significant problems with bladder and bowel function. Some experts favour epidural catheters as an alternative (level 4)

• Epidural steroids +/- bupivacaine may be of use in patients with neuropathic pain, particularly in patients with intractable radicular pain or where systemic opioids have caused severe side effects. However, they may cause significant problems with the bladder and bowel function

• If unilateral pain below the shoulder and prognosis between 3 months and 12 months, consider referral for percutaneous cordotomy (level 3)
Fig 28.1 Approaches to the adjuvant analgesics in neuropathic pain (level 4)
Fig 28.1 Approaches to the adjuvant analgesics in neuropathic pain

Commence Antidepressant or Anticonvulsant of Choice & TITRATE

NO RESPONSE

PARTIAL RESPONSE

Refer SPCT & Consider Pain intervention review

SWITCH DRUG

INSUFFICIENT RESPONSE

NO / PARTIAL RESPONSE

Consider:
- Alternative Drugs / Approaches
- Refer for Intervention assessment if patient well enough

Consider adding second different class of drug
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amitriptyline</strong></td>
<td><strong>Level 1+</strong></td>
<td>10-25mg <strong>nocte</strong> 10mg at night in the elderly. Median preferred dose of 75mg daily</td>
<td>Increase every 3 days as tolerated</td>
<td>Occur in 33% of patients. Include drowsiness and dry mouth Speed of onset 1-7 days. May get improved sleep pattern and mood. Use with caution in the following: cardiac disease; arrhythmias; epilepsy; concurrent use of SSRIs; angle closure glaucoma; history of urinary retention</td>
</tr>
<tr>
<td><strong>Capsaicin 0.075% cream (Level 1-)</strong></td>
<td>Apply topically 3 or 4 times daily</td>
<td>Increase by 100mg-200mg every 3 days. Give in divided doses.</td>
<td>Skin burning and redness</td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>200mg daily. 100mg daily in elderly</td>
<td>Increase by 100mg-200mg every 3 days. Give in divided doses.</td>
<td>Nausea, drowsiness, confusion and ataxia.</td>
<td>Beware of drug interactions.</td>
</tr>
<tr>
<td><strong>Clonazepam</strong></td>
<td>500 micrograms nocte</td>
<td>Increase by 500mcg every 3 days. Maximum dose is 8mg</td>
<td>Sedation</td>
<td></td>
</tr>
</tbody>
</table>

May be given subcutaneously via a syringe driver. May adsorb to PVC so use non PVC equipment for infusions. A CSCI containing clonazepam should only run for a maximum of 12 hours as stability of diluted clonazepam currently only confirmed for 12 hours.
<table>
<thead>
<tr>
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<th>Side effects</th>
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</thead>
<tbody>
<tr>
<td>Dexamethasone (Level 1-) Level 4</td>
<td>8mg daily</td>
<td>Give for 5 days. Discontinue if no response Reduce to lowest dose to maintain effect (see Guidelines on Corticosteroids)</td>
<td></td>
<td>If good response then may benefit from radiotherapy. Monitor blood sugar levels. Consider gastric protection.</td>
</tr>
<tr>
<td>Gabapentin (Level 1+) (Level 1++)</td>
<td>300mg nocte. 100mg nocte if elderly</td>
<td>Increase after 3 days to 300mg bd. Increase to 300mg tds after a further 3 days. Maximum dose is 2400mg. Note: May need to use slower titration regimen e.g. start at 100mg od and increase by 100mg every 2 days</td>
<td>Sedation, dizziness.</td>
<td>Reduce dose in renal failure / impairment. Use in caution in patients with CCF. Diabetic patients may need to adjust hypoglycaemic treatment as weight gain may occur.</td>
</tr>
<tr>
<td>Lidocaine patch (Level 1-)</td>
<td>One strength. Apply for 12 hours daily over painful area and then remove.</td>
<td>Can use up to 3 patches at any one time.</td>
<td>Skin reaction</td>
<td>Current evidence is for post herpetic neuropathic pain. May be useful for post thoracotomy pain.</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Initial dose</td>
<td>Titration</td>
<td>Side effects</td>
<td>Notes</td>
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<tr>
<td>Pregablin (Level 1+) (Level 1++)</td>
<td>Day 1: 25mg od Day 2: 25mg bd Increase every 2 days by 25mg bd</td>
<td>150mg-600mg daily in 2 divided doses. Avoid tds dosing. Treatment costs increase with no benefit.</td>
<td>Sedation, dizziness</td>
<td>Potential pharmacodynamic interactions with all opioids and sedatives. Caution may be required in patients with chronic heart failure. Diabetic patients may need to adjust hypoglycaemic treatment as weight gain may occur.</td>
</tr>
<tr>
<td>Sodium Valproate (Level 2-)</td>
<td>200mg nocte</td>
<td>Increase by 200mg every 3 days. Maximum dose is 1000mg daily.</td>
<td>Nausea, ataxia.</td>
<td></td>
</tr>
</tbody>
</table>
Revised Standards

- All patients with neuropathic pain should be monitored with a pain diary.
- Patients with poorly controlled neuropathic pain should have at least weekly follow-up if an outpatient, and 48\(\text{hourly}\) reassessment if an in-patient.
- If neuropathic pain is escalating (despite optimum medical treatment), an Anaesthetic Pain Specialist should be contacted for advice within 48 hours(?) within 1 week where available.
Discussion
QUESTIONS
• Any addition to Standards?
• Is it worth removing certain adjuvants (e.g. Carbamepine, Valproate)?
• What to recommend when the oral route is not available?
• What to do when a local Anaesthetic pain team is not available?