Neuropathic Agents in Cancer Pain: Do They Work?

Chris Kane
Consultant in Palliative Medicine
Sue Ryder Wheatfields Hospice
Leeds Teaching Hospitals NHS Trust
surely
Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations

Nanna B Finnerup, MD, Nadine Attal, MD, Simon Haroutounian, PhD, Ewan McNicol, MS, Ralf Baron, MD, Robert H Dworkin, PhD, Ian Gilron, MD, Maija Haanpaa, MD, Per Hansson, MD, Troels S Jensen, MD, Peter R Kamerman, PhD, Karen Lund, MD, Andrew Moore, DSc, Srinivasa N Raja, MD, Andrew SC Rice, MD, Michael Rowbotham, MD, Emily Sena, PhD, Philip Siddall, MD, Blair H Smith, MD, and Mark Wallace, MD
• Tramadol NNT 4.7 NNH 12.6
• Opioids NNT 4.3 NNH 11.7
Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain

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

• Rapid titration
• Included a secondary analysis of neuropathic v nociceptive
• NNT 25 NNH 6
Ketamine as an adjuvant to opioids for cancer pain (Review)

Bell RF, Eccleston C, Kalso EA
Overall conclusion

• Not enough evidence
• Multicentre RCT

• Predominately post treatment neuropathic pain

• Previously failed other analgesic treatment

• No benefit and no increase in adverse outcomes

*Fallon et al Jama oncology 04/2018*
Is that surprising?
Schematic representation of the NMDA (N-Methyl-D-Aspartate) receptor complex
Antiepileptic and antidepressant drugs

• Pregabalin and Gabapentin
  • Quoted NNT ~ 4.2 - 6.4

• SNRIs
  • Quoted 6.4

• Amitriptyline
  • Quoted 3.6
Anticonvulsants or Antidepressants in Combination Pharmacotherapy for Treatment of Neuropathic Pain in Cancer Patients

A Systematic Review and Meta-analysis

Jia Guan, MPH, Shiro Tanaka, PhD, and Koji Kawakami, MD, PhD

• Systematic Review
• Mainly cancer induced peripheral neuropathy
<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Mean difference [95%CI]</th>
<th>Mean difference [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rao 2007</td>
<td>-1 2.53 38</td>
<td>-0.6 2.53 39</td>
<td>6.8% -0.40 [-1.53, 0.73]</td>
<td></td>
</tr>
<tr>
<td>Caraceni 2004</td>
<td>-2.4 1.95 79</td>
<td>-2.25 1.8 41</td>
<td>17.7% -0.15 [-0.85, 0.55]</td>
<td></td>
</tr>
<tr>
<td>Vilholm 2008</td>
<td>-1.8 3.54 14</td>
<td>-1.8 3.74 11</td>
<td>1.0% 0.00 [-2.89, 2.89]</td>
<td></td>
</tr>
<tr>
<td>Rao 2008</td>
<td>-0.3 2.53 34</td>
<td>-0.5 2.53 46</td>
<td>6.9% 0.20 [-0.92, 1.32]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal(95%CI)</strong></td>
<td>165</td>
<td>137</td>
<td>32.4% -0.12 [-0.64, 0.39]</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td><strong>P= 0.91; I^2 = 0%</strong></td>
<td></td>
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</tbody>
</table>

| Antidepressants |                   |               |                         |                         |
| Smith 2013      | -1.06 1.61 87     | -0.34 1.62 94 | 39.0% -0.72 [-1.19, -0.25] |                         |
| Gewandter 2014  | -1.14 3.03 227    | -0.83 2.98 231| 28.6% -0.31 [-0.86, 0.24]  |                         |
| **Subtotal(95%CI)** | 314   | 325          | 67.6% -0.54 [-0.94, -0.14] |                         |
| **Heterogeneity:** |                  |              | **P= 0.27; I^2 = 19%**    |                         |

| **Total (95% CI)** | 479   | 462          | 100.00% -0.41 [-0.70, -0.12] |                         |
| **Heterogeneity:** |                  |              | **Tau^2= 0.00; Chi^2=3.54, df=5 (P= 0.62); I^2 = 0%** |                         |
| **Test for overall effect:** | Z=2.73 (P<0.01) |             |                         |                         |
| **Test for interaction:** | P=0.21; I^2 = 36.5% |           |                         |                         |
Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis

Chris M Kane, Matthew R Mulvey, Sophie Wright, Cheryl Craigs, Judy M Wright and Michael I Bennett
### Gabapentin

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caraceni 2004</td>
<td>26.6%</td>
<td>0.04 [-0.39, 0.47]</td>
</tr>
<tr>
<td>Keskinbora 2007</td>
<td>23.7%</td>
<td>0.62 [0.13, 1.11]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>50.3%</td>
<td>0.32 [-0.25, 0.89]</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.11; \chi^2 = 3.03, df = 1 (P = 0.08); I^2 = 67\%

Test for overall effect: \( Z = 1.10 (P = 0.27) \)

### Pregabalin

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercadante 2013</td>
<td>18.9%</td>
<td>-0.38 [-0.99, 0.23]</td>
</tr>
<tr>
<td>Sjorlund 2013</td>
<td>30.7%</td>
<td>0.24 [-0.11, 0.59]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>49.7%</td>
<td>-0.02 [-0.62, 0.58]</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.13; \chi^2 = 2.99, df = 1 (P = 0.08); I^2 = 67\%

Test for overall effect: \( Z = 0.06 (P = 0.95) \)

Total (95% CI) 100.0% 0.16 [-0.19, 0.51]

Heterogeneity: \( \tau^2 = 0.07; \chi^2 = 6.88, df = 3 (P = 0.08); I^2 = 56\%

Test for overall effect: \( Z = 0.90 (P = 0.37) \)
Combinations of Low-Dose Antidepressants and Low-Dose Pregabalin as Useful Adjuvants to Opioids for Intractable, Painful Bone Metastases

Makoto Nishihara, MD¹, Young-Chang P Arai, MD¹, Yoshihiro Yamamoto, PhD¹, Kikuyo Nishida, PhD¹, Maki Arawawa, MD, Takahiro Ushida, MD¹, and Masahiko Ikeuchi, PhD²
Fig. 2. Changes of the daily paroxysmal pain episodes. P, pregabalin. P-I, pregabalin-imipramine. P-M, pregabalin-mirtazapine. Error bar represents standard error of the mean (SEM). * P < 0.05 vs pregablin.
Overall conclusion

• No evidence currently of benefit in cancer tumour pain
• Likely benefit in treatment associated pain
• Need more studies
• May be appropriate to try BUT review regularly
Benzodiazepines

- $\text{GABA}_A$ receptor modulators
- Muscle relaxation
- Anxiolysis
- Clonazepam
Methadone for neuropathic pain in adults (Review)

McNicol ED, Ferguson MC, Schumann R
Methadone for cancer pain (Review)

Nicholson AB, Watson GR, Derry S, Wiffen PJ
’For Pain relief there did not seem to be much difference between methadone and morphine’
Methadone
Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies

Marie T Fallon¹,², Eberhard Albert Lux³,⁴, Robert McQuade⁵, Sandro Rossetti⁵, Raymond Sanchez⁵, Wei Sun⁵, Stephen Wright⁶, Aron H Lichtman⁷ and Elena Kornyeyeva⁵
Evidence

• Consistently low quality

• Very difficult to draw strong conclusions

• Patient selection
The Pain Paradox

*Despite rating their pain as high patients continue to rate their satisfaction of their pain management as high*
Measurement

Nociception -> Interference in daily living -> Poor quality of life
A graphic illustration shows a pain scale ranging from 'No pain' to 'Severe pain'. The scale is divided into 'Mild pain', 'Moderate pain', and 'Severe pain'. Three common pain rating scales are depicted: 'NRS' (Numerical Rating Scale), 'VAS' (Visual Analog Scale), and 'VDS' (Verbal Descriptor Scale). The NRS is marked as going from 0 to 10, with 'No pain' at 0 and 'Worst possible pain' at 10. The VAS is marked with 'Pain as bad as it could possibly be' at the end. The VDS is marked with 'Moderate pain' in the middle.
Original Article

What Patients with Cancer Want to Know
About Pain: A Qualitative Study

Jacqueline L. Bender, BSc; MSc, Joanne Hohenadel, BHSc, Jennifer Wong, BSc,
Joel Katz, PhD, Lorraine E. Ferris, PhD, LLM, Cindy Shobbrook, RN, MN, ACNP,
David Warr, MD, and Alejandro R. Jadad, MD, DPhil, FRCPC

Table 2
Themes

1. Understanding cancer pain
2. Knowing what to expect
3. Options for pain control
4. Coping with cancer pain
5. Talking with others with cancer pain
6. Finding help managing cancer pain
7. Describing pain
Factors Associated with High Satisfaction

- Physician stating importance of pain control
- Receiving instructions to manage pain at home
- Managing side effects
- Allaying fears about addiction


What Happens in Real life?

Figure 2  Triad of elements balanced in cancer pain.
Pain

Nociception

Lack of knowledge and understanding

Poor coping and low expectations

Experience of pain ‘intensity’
No pain | Mild pain | VDS | Moderate pain | Severe pain

0 1 2 3 4 5 6 7 8 9 10

No pain | NRS | Worst possible pain

No pain | VAS | Pain as bad as it could possibly be
Conclusions

Clinically
• Think
• Review

Research
• Time to think again about how we measure ‘Pain’
Thank You