WHO Persisting Pediatric Pain Guidelines: A Research Agenda

Third Partners Meeting on Better Medicines for Children

22 November 2011, Geneva

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World Health Organization
Adequacy Consumption of Opioid Analgesics (2007)

Based on: Seya MJ et al, J Pain & Pall Care Pharmacother 2011;25:6-18
Uses of Controlled Medicines

- Opioid analgesics:
  - e.g. morphine
  - moderate to severe pain

- Long-acting opioid agonists:
  - methadone, buprenorphine
  - treatment of opioid dependence

- Ergometrine and ephedrine:
  - emergency obstetrics

- Benzodiazepines:
  - anxiolytics, hypnotics, antiepileptics

- Phenobarbital:
  - antiepileptic
WHO Cancer Pain and Palliative Care in Children (1998)

- Systematic approach:
  - "By the ladder"
  - "By the clock"
  - "By the appropriate route"
  - "By the individual"

- Three Step Analgesic Ladder

- Obsolete now for some recommended opioids
  - E.g. levorphanol, pethidine

- Not evidence-based / no transparency
WHO Guidelines on Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses

- In Print - Expected Q1 2012
- Evidences-based and transparent
- Focus on pharmacological treatment
  - When opioids – when non-opioids
- 20 treatment guidelines + 4 health systems guidelines
Selected Recommendations

Principle: All moderate and severe pain in children should always be addressed.

- **Two Step Approach** according to the child's level of pain severity.
  
  - First step: paracetamol or ibuprofen (mild pain)  
    - both to be made available
  
  - Second step: morphine (moderate to severe pain)

*Please note: codeine is no longer recommended; tramadol also not recommended*
However...

- For most recommendations:
  - evidence levels assessed "low" and "very low"

- Several clinical questions could not be answered

Research agenda

Published in: *Evidence Based Child Health 6: 1017-1020 (2011)*
Citation

Barbara Milani, Nicola Magrini, Andy Gray, Phil Wiffen and Willem Scholten

WHO Calls for Targeted Research on the Pharmacological Treatment of Persisting Pain in children with Medical Illnesses

Evid.-Based Child Health 6: 1017- 1020 (2011)
www.evidence-basedchildhealth.com
DOI: 10.1002/(ebch.777)
## SRs and RCTs (1)

<table>
<thead>
<tr>
<th>Research Question</th>
<th>SRs and RCTs</th>
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<tbody>
<tr>
<td>2-step vs 3-step; comparison effectiveness of analgesics</td>
<td>2 RCTs, 1 SR of RCTs</td>
</tr>
<tr>
<td>Benefits vs harms of opioids</td>
<td>none</td>
</tr>
<tr>
<td>Comparison effectiveness &amp; harms of strong opioids/routes of administration</td>
<td>9 RTCs</td>
</tr>
<tr>
<td>Opioids rotation and switching</td>
<td>none</td>
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</tbody>
</table>
### SRs and RCTs (2)

<table>
<thead>
<tr>
<th>Description</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>SR vs IR morphine formulations</td>
<td>none</td>
</tr>
<tr>
<td>Episodic or breakthrough pain</td>
<td>none</td>
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<tr>
<td>Adjuvant medicines to relieve pain</td>
<td>none</td>
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</tbody>
</table>
WHO Call for Research

Identified Research Gaps

- Clinical studies needed on paracetamol, NSAIDs and opioid analgesics
  - 8 research topics

- Clinical studies needed on adjuvant medicines for neuropathic pain

- Pharmacokinetics

- Pain assessment tools
Studies on paracetamol, NSAIDs and opioid analgesics (1)

(Pls see publication for details)

- Long term safety data paracetamol and NSAIDS
- Comparisons of strong opioids (effectiveness, safety, feasibility of use in persisting pain)
- Efficacy and safety of intermediate potency opioid analgesics (<12 yrs) e.g. tramadol
- Assessment of two step treatment strategy
Studies on paracetamol, NSAIDs and opioid analgesics (2)

(Pls see publication for details)

- Opioid dose conversion, age group specific
- RCTs of short acting opioids for breakthrough pain
- Opioids rotation policies, including prevention of adverse effects, tolerance and dose escalation)
Studies on adjuvant medicines

(Pls see publication for details)

- Studies on efficacy in neuropathic pain
  - Antidepressants (TCAs, SSRIs, SNRIs)
  - Gabapentin
  - Ketamine (in refractory pain)
Other studies needed

- Pharmacokinetics of opioids and non-opioid analgesics
  - Neonates, infants, children

- Naloxone dosing in opioid tolerant children

- Pain assessment tools
  - Validation of observational behaviour tools in
    - Neonates, infants and preverbal children and children with developmental problems
    - Multidimensional tools
    - Different socio-cultural contexts
Research coordination

- International Childrens Palliative Care Network
  - Executive Director Dr Joan Marston
  - Combining sites for statistical power
  - Registry of ongoing research
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