

WHO Persisting Pediatric Pain Guidelines: A Research Agenda

**Third Partners Meeting on
Better Medicines for Children**

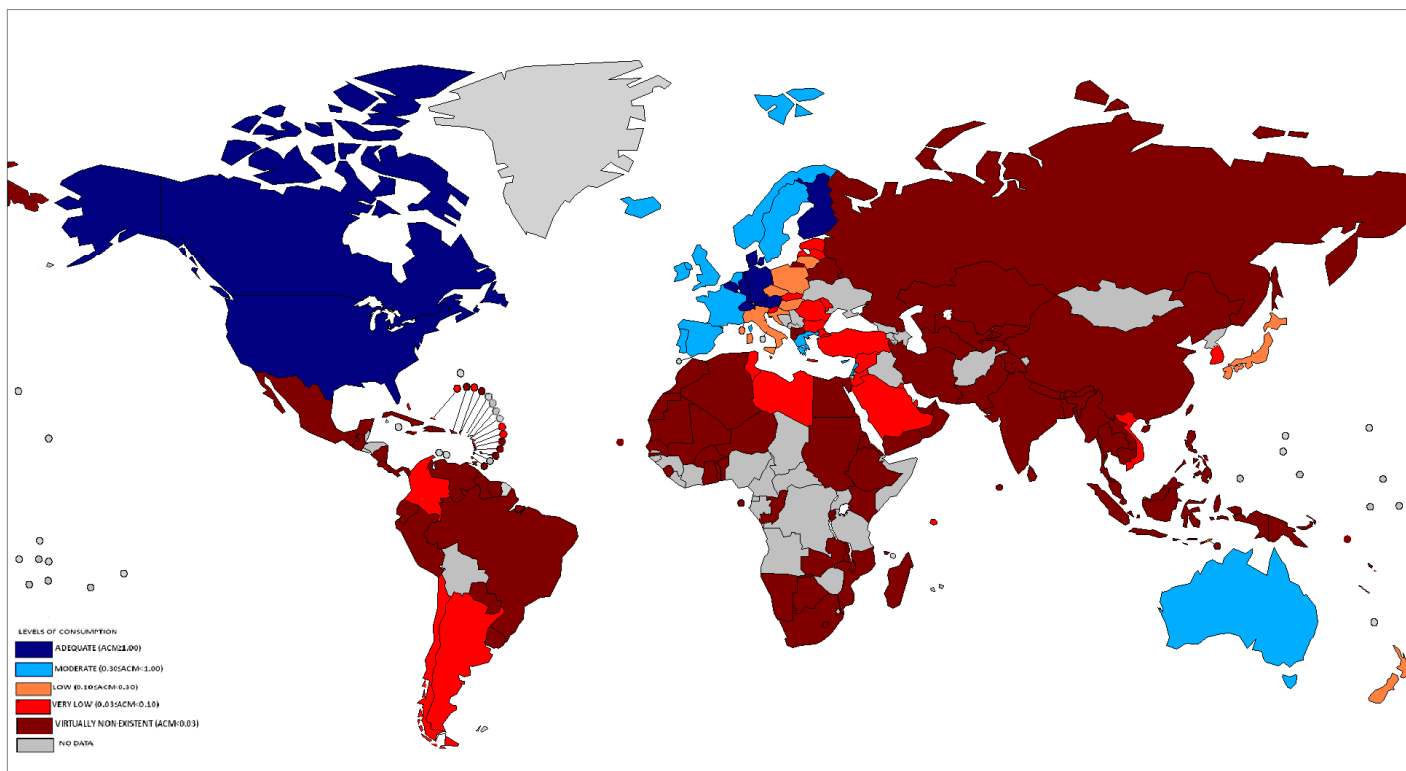
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Adequacy Consumption of Opioid Analgesics (2007)

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



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Data Source: World Health Organization
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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*

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www.evidence-basedchildhealth.com

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SRs and RCTs (1)

2-step vs 3-step; comparison effectiveness of analgesics	2 RCTs 1 SR of RCTs
Benefits vs harms of opioids	none
Comparison effectiveness & harms of strong opioids/routes of administration	9 RTCs
Opioids rotation and switching	none



SRs and RCTs (2)

SR vs IR morphine formulations	none
Episodic or breakthrough pain	none
Adjuvant medicines to relieve pain	none



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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