Do We Still Need a Better Analgesic?
Public Health, Public Policy, and Ethical Perspectives

Richard Payne, M.D.
Professor of Medicine and Divinity
Duke University
April 20, 2012
## Conflict of Interest Disclosure

Richard Payne, MD

<table>
<thead>
<tr>
<th>Item</th>
<th>What was received</th>
<th>My role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grants, Contracts</td>
<td>US Cancer Pain Relief Cmte Cunniff-Dixon Foundation</td>
<td>Sponsor Grantee</td>
</tr>
<tr>
<td>Honoraria and Stock Options</td>
<td>Johnson &amp; Johnson Eli Lilly QRx Pharma Relmada Therapeutics Xanadyne</td>
<td>Member, Scientific Advisory Boards</td>
</tr>
<tr>
<td>Consulting fees</td>
<td>Vitas Innovative Healthcare</td>
<td>Consultant-educational programs; advice to improve access to hospice care</td>
</tr>
</tbody>
</table>
Regina Holliday
The Walking Gallery
http://reginaholliday.blogspot.com/
Pain & Suffering
The Death of Ivan Ilyich

“After supper his friends went home, leaving Ivan Ilyich alone with the knowledge that his life had been poisoned and was poisoning the lives of others, and that far from diminishing, that poison was penetrating deeper and deeper into his entire being”

--p. 71

“They gave him opium and began morphine injections, but this brought no relief.”

--p. 83
Concept of “Total Pain”
Pain as a Biopsychosocial Phenomenon

**EMOTIONAL**
- Guilt
- Why me?
- Life closure issues
- Redemptive Suffering

**SPIRITUAL**
- Loss of function
- Coping abilities

**FINANCIAL**
- Direct costs
- Indirect costs

**PHYSICAL**
- From disease
- From treatment
Underlying Principles of IOM Report

- Pain management is a moral imperative
- Chronic pain can be a disease in itself
- Value of comprehensive treatment
- Need for interdisciplinary approaches
- Importance of prevention
- Wider use of existing knowledge
- The conundrum of opioids
- Rules for patients and clinicians
- Value of public health-and community-based approach
Pain as a Public Health Challenge

Findings

– Pain is a public health problem

• Affects at least 100 million American adults
• Reduces quality of life
• Costs society $560–$635 billion annually
• Federal and state costs almost $100 billion annually
Chronic Pain as a “Disease”

- effects on multiple domains on quality of life
- CNS changes
What is the “Complete” Experience of Pain?
Complexity of Chronic Pain

“The complexity of the “pain web” in the brain indicates the difficulty that comes with evaluating a multidimensional experience such as pain and pain affect…Patients present with one or more actual pain generators, a wide range of past life experience in dealing with pain and suffering, and with their own natural proclivities and resources for handling their pain burden. Successful clinical and research outcomes must be capable of addressing or controlling for such wide variability.

p. 220

--Director of a pelvic pain specialty center
Essentially all studies and evidence-based reviews indicate that currently available analgesic agents provide incomplete pain relief for conditions including cancer, neuropathic pains and various other chronic pains.

Cochrane Reviews

Eisenberg E et al. Opioids for neuropathic pain. 2009
Wiffen M et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. 2011
Wiffen M et al. Oral morphine for cancer pain. 2010
Noble M et al. Long term opioid management for chronic non-cancer pain. 2010
Medical Professionalism

Principles

• Fundamental principles
  – Fiduciary responsibility of physicians
  – Trustworthiness

• Critical corollary values
  – Competency
  – Caring
  – Confidentiality
  – Nonjudgmental and nonsexual regard of patients
Medical Professionalism
Core Elements

• Essential Elements
  – Devotion to medical service
  – Public profession of values
  – Negotiation of professional and social values
    “the social contract”

• Critical corollary values
  – Stewardship
  – Accountability
Medical Professionalism
Accountability

• Dominant models
  – Professional
  – Economic
  – Political

• Caveats
  – One model does not apply to all healthcare
  – Cannot confuse models
Do we need better analgesics?

YES!

But analgesic responsiveness is only one component of the pain experience
Duke Divinity School

“Be transformed by the renewing of your mind”
Pain Phenotype

Symptoms
Signs
Biomarkers/Biosignatures
Mood, behavior, sleep, performance
Quality of Life
Response to treatment
Response to injury
Pain Genotype
Pain variance - 50% heritable

Rare mutations
Common polymorphisms

Pain intensity
Pain chronicity
Response to treatment
Properties of an Ideal Analgesic

The holy grail of pain research

• Completely safe & totally effective
• Works on all pains
• Tolerance does not develop
• Non-addicting
Proportion of Patients with at least 50% Pain Relief, Oral Opioids, Follow-up 7.5 months (mean) to 13 months ($I^2=77.3\%$)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Statistics for each study</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event rate</td>
<td>Lower limit</td>
</tr>
<tr>
<td>Zenz 1992</td>
<td>0.510</td>
<td>0.413</td>
</tr>
<tr>
<td>Allan 2005</td>
<td>0.392</td>
<td>0.341</td>
</tr>
<tr>
<td></td>
<td>0.443</td>
<td>0.333</td>
</tr>
</tbody>
</table>

Data for Allan 2005 pain improvement on movement, which had the largest proportion of patients achieving at least 50% pain relief for oral opioids. Proportion of patients achieving average overall pain reduction not reported.

Discontinuation from Oral Opioids Studies due to Insufficient Pain Relief, Follow-up 7 to 24 months (mean) ($I^2=81.8\%$)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klapetek 1971</td>
<td>0.045</td>
<td>0.003</td>
<td>0.448</td>
<td>0 / 10</td>
</tr>
<tr>
<td>Zenz 1992</td>
<td>0.210</td>
<td>0.141</td>
<td>0.301</td>
<td>21 / 100</td>
</tr>
<tr>
<td>Harati 2000</td>
<td>0.099</td>
<td>0.058</td>
<td>0.163</td>
<td>13 / 131</td>
</tr>
<tr>
<td>Roth 2000</td>
<td>0.188</td>
<td>0.130</td>
<td>0.263</td>
<td>25 / 133</td>
</tr>
<tr>
<td>Caldwell 2002</td>
<td>0.153</td>
<td>0.116</td>
<td>0.198</td>
<td>45 / 295</td>
</tr>
<tr>
<td>Allan 2005</td>
<td>0.044</td>
<td>0.027</td>
<td>0.071</td>
<td>15 / 342</td>
</tr>
<tr>
<td>McIlwain 2005</td>
<td>0.079</td>
<td>0.059</td>
<td>0.107</td>
<td>39 / 491</td>
</tr>
<tr>
<td>Pascual 2007</td>
<td>0.094</td>
<td>0.078</td>
<td>0.113</td>
<td>99 / 1052</td>
</tr>
<tr>
<td>Portenoy 2007</td>
<td>0.102</td>
<td>0.065</td>
<td>0.159</td>
<td>17 / 166</td>
</tr>
<tr>
<td>Thorne 2008</td>
<td>0.040</td>
<td>0.015</td>
<td>0.102</td>
<td>4 / 100</td>
</tr>
<tr>
<td></td>
<td>0.103</td>
<td>0.076</td>
<td>0.139</td>
<td></td>
</tr>
</tbody>
</table>

For studies with no events, a correction factor of 0.5 is added to both numerator and denominator to enable analysis.

### Review: Opioids for neuropathic pain
#### Comparison: 1 Short-term Efficacy Studies: Opioid vs. Placebo
#### Outcome: 1 Pain intensity post opioid/placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opioid N</th>
<th>Mean(SD)</th>
<th>Placebo N</th>
<th>Mean(SD)</th>
<th>Mean Difference IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Peripheral Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kupers 1991b</td>
<td>8</td>
<td>28 (14)</td>
<td>8</td>
<td>40 (28)</td>
<td>-12.00 [-33.69, 9.69]</td>
<td>9.7%</td>
<td></td>
</tr>
<tr>
<td>Rowbotham 1991</td>
<td>19</td>
<td>32.6 (33.2)</td>
<td>19</td>
<td>43.6 (29.3)</td>
<td>-11.00 [-30.91, 8.91]</td>
<td>11.5%</td>
<td></td>
</tr>
<tr>
<td>Wu 2002a</td>
<td>20</td>
<td>30 (22.4)</td>
<td>20</td>
<td>46 (22.4)</td>
<td>-16.00 [-29.88, -2.12]</td>
<td>23.6%</td>
<td></td>
</tr>
<tr>
<td>Wu 2002b</td>
<td>22</td>
<td>32.6 (18)</td>
<td>22</td>
<td>50.1 (25.5)</td>
<td>-17.50 [-30.54, -4.46]</td>
<td>26.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>69</td>
<td></td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.6</td>
<td>43.6</td>
<td>-15.22 [-23.19, -7.24]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.39, df = 3 (P = 0.94); I² = 0.0%

Test for overall effect: Z = 3.74 (P = 0.00018)

| 2 Central Pain    |          |          |           |          |                               |        |                               |
| Attal 2002        | 15       | 33 (23)  | 15        | 52 (19)  | -19.00 [-34.10, -3.90]        | 20.0%  |                               |
| Kupers 1991a      | 6        | 43 (13)  | 6         | 58 (26)  | -15.00 [-38.26, 8.26]         | 8.4%   |                               |
| **Subtotal (95% CI)** | 21      |          | 21        |          |                               |        |                               |
|                   |          | 43.6      | 58 (26)   | -17.81 [-30.48, -5.15]        |        |                               |

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0.0%

Test for overall effect: Z = 2.76 (P = 0.0058)

| **Total (95% CI)** | 90      |          | 90        |          |                               |        |                               |
|                   |          |          |           |          |                               |        |                               |
|                   |          | 32.6      | 58 (26)   | -15.96 [-22.70, -9.21]        |        |                               |

Heterogeneity: Chi² = 0.58, df = 5 (P = 0.99); I² = 0.0%

Test for overall effect: Z = 4.63 (P < 0.00001)

Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0.0%
### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Gabapentin</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.5.1 Postherpetic neuralgia</td>
<td>Irving 2009</td>
<td>49</td>
<td>107</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Rice 2001</td>
<td>86</td>
<td>223</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Rowbotham 1998</td>
<td>47</td>
<td>113</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Wallace 2010</td>
<td>99</td>
<td>269</td>
<td>31</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>712</td>
<td>409</td>
<td>31.5%</td>
<td>1.84 [1.50, 2.26]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>281</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 7.17, df = 3 (P = 0.07); I² = 58%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.81 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1.5.2 Painful diabetic neuropathy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Gabapentin</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Backonja 1998</td>
<td>47</td>
<td>84</td>
<td>25</td>
<td>81</td>
</tr>
<tr>
<td>CTR 945-1008</td>
<td>113</td>
<td>200</td>
<td>77</td>
<td>189</td>
</tr>
<tr>
<td>CTR 945-224</td>
<td>72</td>
<td>166</td>
<td>26</td>
<td>77</td>
</tr>
<tr>
<td>Gorson 1999</td>
<td>17</td>
<td>40</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>Simpson 2001</td>
<td>15</td>
<td>30</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>520</td>
<td>417</td>
<td>45.0%</td>
<td>1.50 [1.28, 1.75]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>264</td>
<td>144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.55, df = 4 (P = 0.47); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.06 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI) | 1620        | 1211     | 100.0%    | 1.68 [1.51, 1.88] |
| Total events   | 695         | 310      |            |            |
| Heterogeneity: Chi² = 15.73, df = 13 (P = 0.26); I² = 17% |
| Test for overall effect: Z = 9.29 (P < 0.000001) |
| Test for subgroup differences: Not applicable |
Multiple chronic pain states are associated with a common amino acid–changing allele in KCNS1
Overcoming obstacles to developing new analgesics

Clifford J Woolf

LIST THE STRATEGIES NOTED BY WOOLF
Multiple chronic pain states are associated with a common amino acid–changing allele in KCNS1

Murkerjee book
Naivety of thinking that there would be a single drug for all cancers
Atul J. Butte of Stanford can map diseases using data from gene chips that measure which genes are active in a cell.

The “diseasome”

The “Connectivity Map”
Pain as a Public Health Challenge
Findings-2

– More consistent data on pain are needed to:

• Monitor changes in incidence and prevalence
• Document rates of treatment and undertreatment
• Assess health and societal consequences
• Evaluate impact of changes in policy and care
Pain as a Public Health Challenge
Findings-3

– A population-based strategy is needed to reduce pain and its consequences. It should:

• Heighten national concern about pain

• Use public health strategies to foster patient self-management

• Inform public about nature of pain

• Focus on pain prevention
Figure 1: Global Per Capita Consumption of Morphine, 2000

MORPHINE CONSUMPTION (MG/CAPITA)

<table>
<thead>
<tr>
<th>Country</th>
<th>MORPHINE CONSUMPTION (MG/CAPITA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>69.36</td>
</tr>
<tr>
<td>Canada</td>
<td>51.02</td>
</tr>
<tr>
<td>United States of America</td>
<td>29.53</td>
</tr>
<tr>
<td>Chile</td>
<td>2.64</td>
</tr>
<tr>
<td>Brazil</td>
<td>2.42</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>1.95</td>
</tr>
<tr>
<td>Argentina</td>
<td>1.64</td>
</tr>
<tr>
<td>Uruguay</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Sources
Consumption data: International Narcotics Control Board
Population data: United Nations Demographic Yearbook, 2000

Professionalism in Health Care

• Professionalism
  – “In the highly regimented, regulated, or restrictive environment, medical practice can frustrate, oppress, and enslave—unless the physician holds his noble purpose uppermost in mind.”
    Lois DeBakey
    *Medicine: Preserving the Passion in the 21st Century*
    Springer, 2004, p. 1

  – “Competence...is an important sign of ..compassion”
    Willis Hurst
    (Quoted in *Medicine: Preserving the Passion in the 21st Century*, p. 7)
Professional Formation of Physicians

- Grounded in biology and scientific method
- Professional standards and ethics
  - Utilitarian
  - Moral
    - e.g., obligation to attend to pain and suffering
- Competencies
  - Traditional
  - “Narrative” (esp. those attending to chronic disease)
Pain & Suffering

“The greatest evil is physical pain.”

— St. Augustine [354-430]
Soliloquies, I.21