OPIOIDS IN CHRONIC NON-CANCER PAIN

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Analgesic drugs: therapeutic considerations

- NSAIDs often have inadequate analgesic effects
- Contraindications
- Adverse effects requiring discontinuation
- Opioid use can reduce the dosage of NSAIDs and their toxicity
- The anti-inflammatory effects of DMARDs often take weeks to months to develop
<table>
<thead>
<tr>
<th></th>
<th>Weighted Total</th>
<th>UK (n=300)</th>
<th>France (n=300)</th>
<th>Germany (n=302)</th>
<th>Italy (n=300)</th>
<th>Spain (n=301)</th>
<th>Poland (n=300)</th>
<th>Sweden (n=300)</th>
<th>Norway (n=304)</th>
<th>Denmark (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>44%</td>
<td>23%</td>
<td>25%</td>
<td>54%</td>
<td>68%</td>
<td>49%</td>
<td>71%</td>
<td>27%</td>
<td>24%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Weak Opioids</strong></td>
<td>23%</td>
<td>50%</td>
<td>19%</td>
<td>20%</td>
<td>9%</td>
<td>13%</td>
<td>28%</td>
<td>36%</td>
<td>50%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Paracetamol</strong></td>
<td>18%</td>
<td>38%</td>
<td>38%</td>
<td>2%</td>
<td>6%</td>
<td>8%</td>
<td>8%</td>
<td>26%</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>COX-2 Inhibitors</strong></td>
<td>6%</td>
<td>3%</td>
<td>6%</td>
<td>8%</td>
<td>7%</td>
<td>2%</td>
<td>1%</td>
<td>7%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Strong Opioids</strong></td>
<td>5%</td>
<td>12%</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
<td>1%</td>
<td>4%</td>
<td>3%</td>
<td>6%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Source: Q19. Which prescription pain medicines are you currently taking for the specific pain we have been discussing? (most common mentions)
OPIOIDS IN NEUROPATHIC PAIN

ARNER 1988  LACK OF ANALGESIC EFFECT OF OPIOIDS ON NEUROPATHIC & IDHIOPATHIC PAIN

PORTENOY 1990  THE NATURE OF OPIOID RESPONSIVENESSNESS AND ITS IMPLICATION FOR NEUROPATHIC PAIN: NEW HYPOTHESES DERIVED FROM STUDIES OF OPIOID INFUSIONS

ROWBOTHAM 1991  BOTH INTRAVENOUS LIDOCAINE AND MORPHINE REDUCE THE PAIN OF POST-HERPETIC NEURALGIA

JADAD 1992  MORPHINE RESPONSIVENESSNESS OF CHRONIC PAIN: DOUBLE-BLIND RANDOMISER CROSS-OVER STUDY WITH PATIENT-CONTROLLED ANALGESIA

MCQUAY 1992  OPIOID SENSITIVITY OF CHRONIC PAIN: A PATIENT-CONTROLLED ANALGESIA METHOD

WATSON 1998  EFFICACY OF OXYCODONE IN NEUROPATHIC PAIN. A R-DB-CR TRIAL IN PHN
EFFICACY OF OXYCODONE IN NEUROPATHIC PAIN

Watson - Neurology, 1998

POST-HERPETIC - 50 PTS
20-60 mg - DB - CROSSOVER 4 WEEKS

• PAIN INTENSITY
• ALLODYNIA
• PAROXYSMAL PAIN
• DISABILITY
Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Watson et al, Pain 2003

CO C design 36 pts
Oxycodone SR 10-40mg v benztropine 0.25-1mg
4 weeks CO. Acetaminophen rescue 325-650 mg/4-6h

Oxycodone
Daily pain, steady pain, brief pain, skin pain, total pain, disability, quality of life scores, mental component
NNT = 2.6
90% open-label at 6 mos
63% at 1 yr
Opioids versus antidepressants in postherpetic neuralgia. Raja et al, Neurology 2002

- 76 pts DB C CO trial
- 8 weeks each, 1 week wash-out
- A - SR morphine 15 mg (methadone), titration
- B - nortriptyline 10 mg (desipramine), titration
- C - placebo
Opioids versus antidepressants in postherpetic neuralgia. Raja et al, Neurology 2002

- Morphine titration 91 mg in 4.4 weeks
- Nortriptyline titration 89 mg in 4.1 weeks
- Placebo titration in 3.6 weeks
- More pts dropped out with morphine
- TCA worsened performance
- Pain reduction with morphine
- Preference opioids 54%, TCA 30%
- Responders: 52% opioids, 34% TCA
- NNT morphine 2.7 - TCA 4

- 81 pts refractory to treatment- levorphanol cps
- DB C design: 0.75mg v 0.15 mg maximum 21 cps/day for 8 weeks
- 0.75 mg pain reduction 36% (8.9 mg)
- 0.15 mg pain reduction 21% (2.7mg)
- Affective distress, functioning, sleep (no differences)
- Central pain after stroke
- More adverse effects with higher doses

- Key outcome opioid treatment aims: pain relief, improved QoL, improved functional capacity
- 16684 pts (10066 took part) chronic non-cancer pts.
- Cross-sectional of opioid users v non-users

- Opioid usage was significantly associated with reporting of moderate-severe pain, poor self-rated health, not being engaged in employment, higher use of health care system, and a negative influence on QoL.
Comparative efficacy and safety of LA oral opioids for chronic non cancer pain: a systematic review.
Chou et al JPSM 2003

- 16 randomized trials 1427 pts - no good quality
- 8 observational studies 1190 pts – poorer quality

- No differences among opioids, equally effective
Opioids in chronic non-cancer pain: a systematic review of efficacy and safety. Kalso et al, Pain 2004

- 15 DB studies
- 30% decrease in PI, comparable in NP and MP.
- 80% experienced AE
- Only 44% pts on open label were still on opioids.
- Small number of pts and short follow up.
Come dico a mia moglie che mi sono perso se non ricordo nemmeno il numero di casa?
NO SIGNS OF COGNITIVE IMPAIRMENT

COGNITIVE BENEFIT OF PAIN RELIEF

PAIN MAY HAVE AN IMPACT ON COGNITIVE FUNCTION
EFFECTS OF LONG-TERM OPIOID THERAPY ON PSYCOMOTOR FUNCTION IN PTS WITH CANCER PAIN OR NON MALIGNANT PAIN

Larsen, 1999

- **OPIOIDS**
  - CANCER
  - NON CANCER
- **NON-OPIOIDS**
- **CONTROL**

OPIOIDS PRODUCE A SLIGHT IMPAIRMENT OF NP + AGE + CANCER PAIN
NEUROPSYCHOLOGICAL PERFORMANCE IN CANCER PTS: THE ROLE OF ORAL OPIOIDS, PAIN AND PERFORMANCE STATUS

Sjogren, 2000

CONTROL A
CONTROL B
PAIN B
PAIN OPIOID B
OPIOID B

(GOOD K)
(BAD K)

PAIN, K MAY AFFECT NP AND NOT OPIOIDS “PER SE”
MORPHINE 209 mg - CONTROL

ONLY DIFFERENCE IN BALANCING ABILITY WITH CLOSED EYES
EFFECTS OF OPIOIDS ON DRIVING ABILITY ON OPIOIDS-CEREBRALLY COMPROMISED

Galski - 2000

TESTS

PERCEPTION

COGNITION

COORDINATION

BEHAVIOR

DIFFICULTIES IN FOLLOWING INSTRUCTIONS

IMPULSIVITY

EFFECTS OF OPIOIDS ON DRIVING ABILITY ON OPIOIDS-CEREBRALLY COMPROMISED

Galski - 2000

TESTS

PERCEPTION

COGNITION

COORDINATION

BEHAVIOR

DIFFICULTIES IN FOLLOWING INSTRUCTIONS

IMPULSIVITY
Driving ability under long-term treatment with TTS fentanyl
Sabatowski et al, JPSM 2003

Stable dose for 2 weeks
30 pts compared with 90 volunteers

- No difference in performance measures.
- The threshold for fitness to drive (German law) did not differ between groups.


27 pts taking less than 15 mg oxycodone (plus acetaminophen)
TTD fentanyl 25 mcg/h titrated against pain
End titration: mean dose 50 mcg/h.
3 pts discontinued for adverse effects
No differences in driving simulation measures

- 28 pts (40-140 mg)
- 18 continued, 10 stopped (control group)
- No impairment of any neuropsychological variable
- Correlation between pain relief, mood and improvement of memory
- Persisting effect on pain, and at a less extent on QoL and mood
- No impairment in NP performance.
- Memory improved in responders
- Adverse effects increased in time
Drug abuse

- Unsanctioned drug use, irrespective of consequences and in excess of that required for analgesia
Addiction

- Primary, chronic, psychosocial disease, with genetic, psychological and environmental factors influencing its development and manifestations.
- Behavior: impaired control over drug use, compulsive use, continued use despite harm, and craving.
- Exposure to drugs is only one of the etiologic factors.
Predictors of aberrant drug-related behavior and addition

- Lack of large epidemiologic surveys for a meaningful time period (1 yr)

Addiction arises from a complex set of influences:
- Genetic
- Psychiatric
- Familial
- Social
- Spiritual
- Chemical
Physical dependence

- Induced by administration of an antagonist
- It is an expected outcome of regular use, even for relatively short term (normal response)
- It may develop with many substances, B-blockers, alpha-2 agents, steroids, antidepressants, etc.
- It does not indicate addiction, but it is problematic.
- State of adaptation (including tolerance) manifested by a drug-class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of drug, and/or
Tolerance

- State of adaptation resulting in a reduction of one or more effects (both desired or undesired) over time (normal response)
- Developing at different rates. Ex. Tolerance develops more slowly to analgesia than to respiratory depression, and tolerance to constipation may never occur
- Tolerance to analgesia is variable and not absolute
- It may be problematic

- Degenerative diseases - mean duration 10 yrs
- Amitriptyline 65% - Paracetamol 29% - NSAIDs 11%
- 45 pts on strong opioids (33 morphine, 11 fentanyl, et al)
- 92% starting low doses (<60 mg)
- 48% increased their dose
- 24% reduced their dose
- 29% same dose
- 54% remained in the range of 60 mg
- Duration on strong opioids 14 mos,

Stopping opioids

- 56% ceased opioid therapy (44% within first 6 mos)
- 22% fear of addiction, 19% alternative therapy, 47% adverse effects, ineffectiveness 8%
- 66% reported worsening pain, 50% decrease in physical function
- 16% reported withdrawal symptoms at cessation
- 2 pts felt to be addicted
- 69% felt they health suffered taking opioids, 39% would continue regardless their health suffering
Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. Rajagopal et al, JPSM 2003

- 20 cancer pts, disease free > 1 yr, on >200 mg morphine equivalents
- Sexual Desire score 1-5/10
- < testosterone levels without compensation of FSH, LH
- Central hypogonadism and sexual dysfunction
- > prolactin, gonadotrophine secretion
Established place in cancer pain
Controversial use in non-malignant pain
Opioids hardly mentioned in therapeutic guidelines
Restrictive approach due to risks of tolerance, adverse effects, dependence
Positive experience in some pts
Long-term use for non-cancer pain can be justified if some rules and precautions are observed
Start low, go slow

- Pharmacokinetic considerations
- Pharmacodynamic considerations
- Concomitant medications
GUIDELINES FOR OPIOID THERAPY IN NON MALIGNANT PAIN
Portenoy RK

AFTER ALL REASONABLE ATTEMPTS
CONTRAINDICATIONS: HISTORY, CHARACTER, ENVIRONMENT
SINGLE RESPONSIBILITY
INFORMED CONSENT
DRUGS AROUND THE CLOCK - TITRATION
PROMPT REASSESSMENT (FAILURE WITH LOW DOSES)
EMPHASIS ON PHYSICAL AND SOCIAL FUNCTION
EXTRA DOSES
INITIAL ONE MONTHLY VISIT
EXACERBATIONS OF PAIN → HOSPITALIZATION
ABERRANT BEHAVIORS
MONITORING (PAIN ADVERSE EFFECTS - STATUS - BEHAVIOR)
SELF-REPORT ADVISABLE
DOCUMENTATION
Basic rules of opioid therapy

- Begin with weak opioids and then progress to strong opioids
- Dosage should follow a fixed daily schedules
- Individual dose titration should be carried out over 4 weeks
- Avoid additional parenteral boluses
- Prescribe oral or transdermal medication
- Use slow release preparations
- Adverse effects should be adequately treated
- Emergency medication for breakthrough pain should be defined
- A pain diary should be kept
SITUATIONS FOR CONSIDERING DISCONTINUATION OF OPIOID THERAPY

- A lack of response to opioid therapy during test phase (non-responders)
- Insufficient pain reduction
- Uncontrolled dosage increase
- Poor compliance with drug intake
- Intake of non-prescribed medication
- Lack of improvement in activity and mobility
- Clear addiction behaviour
Angels or devils...

- Meanly, about 1/3 of patients not responsive to previous treatments can benefit from opioid therapy, and individualized treatment may increase these figures
- No data on combination therapy
- Difficulties in monitoring pts
- Psychological implications
- Data from long-term studies are lacking with respect to the hormonal changes
Per sfuggire una tentazione...

... occorre affrontarla
<table>
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<tr>
<th>Effect</th>
<th>3 months (n = 21)</th>
<th>6 months (n = 17)</th>
<th>12 months (n = 11)</th>
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<tbody>
<tr>
<td>Constipation</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Subjective memory impairment</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
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<td>1</td>
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<table>
<thead>
<tr>
<th></th>
<th>Morphine treated group</th>
<th>Control group</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td>VAS</td>
<td>61 ± 21</td>
<td>45 ± 21**</td>
</tr>
<tr>
<td>McGill (S)</td>
<td>19 ± 7</td>
<td>17 ± 9</td>
</tr>
<tr>
<td>McGill (A)</td>
<td>17 ± 5</td>
<td>14 ± 6*</td>
</tr>
<tr>
<td>W-VAS</td>
<td>60 ± 22</td>
<td>44 ± 24*</td>
</tr>
<tr>
<td>BDI</td>
<td>12 ± 6</td>
<td>8 ± 5*</td>
</tr>
<tr>
<td>HDRS</td>
<td>12 ± 5</td>
<td>8 ± 5*</td>
</tr>
<tr>
<td>Spielberger</td>
<td>23 ± 13</td>
<td>19 ± 12</td>
</tr>
</tbody>
</table>

There was a significant effect of time on the affective scores of the McGill pain questionnaire ($P < 0.05$ from 3 to 12 months) and on the BDI ($P < 0.05$ at 3 months) (repeated measures ANOVA). In comparison with the control group, there was a significant effect of morphine at 3 months on the present pain scores ($F = 7.2; P = 0.01$), W-VAS ($F = 5.1; P = 0.03$) and HDRS scores ($F = 4; P = 0.05$) (repeated measures ANOVA). *$P < 0.05$; **$P < 0.01$ in comparison with baseline values (Wilcoxon signed rank test).

Problematic opioid use (104 pts) 3 pts judged addicted

- 1 abused drugs
- 4 severe physical withdrawal symptoms at discontinuation
- 72 pts health had suffered, 41 would continue
- 80 pts adverse effects
- 28 ceased because of side effects