Opioids – silent killers?

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Does it depend on the situation?
Who thinks opioids affect survival in cancer pain?

Positively
Negatively

How?

Does it depend on the opioid?
Overview

• What are opioids?
  – Are all opioids the same?
  – How do opioids work?
• Why would opioids affect survival
• Do opioids affect survival
• Implications in the palliative medicine setting
What are opioids?

- Chemically diverse molecules
- Common property - activate opioid receptor
- Disparate physicochemical and pharmacological properties
  - Act in different ways on the opioid receptor
  - Act via non-opioid receptors
Opioids have many intracellular effects

- PKC
- MAPK
- ↑NO
- ↑cGMP
- ATP
- ↓cAMP
- PKA

Gene Regulation

- GPCR
- α GDP
- βγ
- K⁺
- Ca²⁺
- VGCC
Biological roles of opioids

• Endogenous opioids
  – Homeostasis
    • pain modulation, GI tract regulation, hormonal and immune modulation

• Exogenous (prescribed) opioids
  – Pain, diarrhoea, cough, dyspnoea, addiction
## Effects of opioids on different organ systems

<table>
<thead>
<tr>
<th>System</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Constipation, xerostomia, nausea and vomiting, delayed gastric emptying, gastro-oesophageal reflux, constriction of the sphincter of Oddi</td>
</tr>
<tr>
<td>Neurological</td>
<td>Analgesia, delirium, hallucinations, sedation, myoclonus, hyperalgesia, seizures, headaches, euphoria, dysphoria, dependency</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Bradycardia, hypotension</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Respiratory depression, decreased cough reflex, non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Urological</td>
<td>Urine retention, decreased urine production</td>
</tr>
<tr>
<td>Endocrinological</td>
<td>Hypogonadism/sexual dysfunction, osteoporosis</td>
</tr>
<tr>
<td>Immunological</td>
<td>Possible effects on neutrophil, macrophage, natural killer cell, T cell and cytokine function</td>
</tr>
</tbody>
</table>
How opioids affect survival - Acute

Adapted from Boland et al, Pain 2015
How opioids affect survival - Chronic

Apoptosis

- sigma-2 receptor
  - Crawford and Bowen 2002
- p53/p53-dependent
  - p21, Bax, Fas
  - Tegeder et al. 2003
- Caspase 3/9
- Cytochrome c
  - Bim/Bcl-2

Immune response

- Anti-inflammatory cytokines (IL-4)
  - Roy et al. 2005
- Pro-inflammatory cytokines (TNF, IL-6, IL-2)
  - Bonnet et al. 2008
  - Börner et al. 2009
- Activity of NK
  - Sacerdote et al. 1997

Morphine

- JNK
  - (+)
  - Lin et al. 2009
- ROS
  - (-)
- NO → MMPs → ECM
  - Gach et al. 2011
- COX-2
- VEGF
  - (+)
  - Balsubramanian et al. 2001
- Angiogenesis
  - (+)
  - Gupta et al. 2002, Chen et al. 2006
- PGE₂
  - Farooqui et al. 2007

Metastasis

(+) Stimulation
(-) Inhibition
Immune effects are just one piece of the overall effect.
How opioids affect survival

Boland et al, Pain 2015
Opioid immune interactions

Boland et al, BJC 2014
A preliminary evaluation of the effects of opioids on innate and adaptive human in vitro immune function

Jason W Boland,¹,² Gemma A Foulds,¹ Sam H Ahmedzai,¹
A Graham Pockley¹,³

- Methadone, oxycodone and diamorphine inhibited the production of IL-6 by IL-2 stimulated PBMCs
- Anticancer immunity unaffected
Opioid immune interactions

Boland et al, BJC 2014
How opioids affect survival

Boland et al, Pain 2015
Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review

J W Boland*, K McWilliams, S H Ahmedzai and A G Pockley
Findings

• Five human studies, assessed the effects of opioids (all morphine) on the immune system in patients with cancer
• All evaluated the effect of on immunologic end points – effects variable
• None measured clinical effects
How opioids affect survival

Acute effects

Respiratory depression
Prolonged QTc interval

Chronic effects

Apoptosis
Angiogenesis
Immunity

Pain

Opioids

Cancer

Survival

Boland et al, Pain 2015
Is regular systemic opioid analgesia associated with shorter survival in adult patients with cancer? A systematic literature review

Jason W. Boland, Lucy Ziegler, Elaine G. Boland, Kirstine McDermid, Michael I. Bennett

Systematic review methodology

*a priori* protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

- Embase
- MEDLINE(R)
- Web Of Science
- CINAHL
- ClinicalTrials.gov
- Conference Proceedings Citation Index
- International Clinical Trials Registry Platform
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effect
- Cochrane Central Register of Controlled Trials
- NHS Economic Evaluation Database
Inclusion criteria

Studies which assessed the effect of opioids on survival of adults with cancer

RCTs, cohort studies, prospective and retrospective observational studies, and database analysis
Exclusion criteria

Surgery (eg, opioids for perioperative pain)
Opioids taken recreationally
Opioids used for addiction

Study types: case studies
<table>
<thead>
<tr>
<th>Database</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase</td>
<td>322</td>
</tr>
<tr>
<td>Ovid MEDLINE</td>
<td>276</td>
</tr>
<tr>
<td>Web of Science</td>
<td>40</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
<td>2</td>
</tr>
<tr>
<td>International Clinical Trials Registry</td>
<td>10</td>
</tr>
<tr>
<td>CINAHL</td>
<td>29</td>
</tr>
<tr>
<td>Cochrane Database of Systematic Reviews</td>
<td>25</td>
</tr>
<tr>
<td>Cochrane Central Register of Controlled Trials</td>
<td>43</td>
</tr>
<tr>
<td>Database of Abstracts of Reviews of Effect</td>
<td>1</td>
</tr>
<tr>
<td>NHS Economic Evaluation Database</td>
<td>1</td>
</tr>
</tbody>
</table>

**Identification**

- Records identified through database searching (n = 749)
- Additional records identified through other sources (n = 32)
- Records after duplicates removed (n = 526)
Records after duplicates removed (n = 526)

Records screened (n = 526)

Records excluded (n = 485)

Full-text articles excluded (n = 21)
- Did not assess effect of opioids on survival (n=9)
- Recreational opioid use (n=2)
- Incomplete data summary (n=8)
- Abstracts only (n=2)

Full-text articles assessed for eligibility (n = 41)

Studies included in qualitative synthesis (n = 20)
End of life studies (last days or weeks of life)

- 13 studies
- GRADE criteria: 11 very low and 2 low quality
- 11 retrospective studies and 2 secondary data analysis
- mean sample size was 254 patients
- Some just measured opioid dose in last days of life
<table>
<thead>
<tr>
<th>Study</th>
<th>Research question/aim</th>
<th>Study design</th>
<th>Patient population/setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of life studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bercovitch et al.⁹; high-dose morphine use in the hospice setting. A database survey of patient characteristics and effect on life expectancy</td>
<td>What are the characteristics of patients requiring high-dose morphine and the effect on survival?</td>
<td>Retrospective review</td>
<td>453 patients (from 651; 70%) on morphine with mixed cancers admitted to a hospice in Israel</td>
</tr>
<tr>
<td>Thoms and Sykes⁷³; opioid use in last week of life and implications for end-of-life decision-making</td>
<td>Is symptom control with opioids associated with shortening of life in palliative care?</td>
<td>Retrospective review</td>
<td>Of 238 consecutive patients dying in a UK hospice, 212 (89%) received opioids in the last 24 h of life</td>
</tr>
<tr>
<td>Morita et al.⁵³; effects of high-dose opioids and sedatives on survival in terminally ill cancer patients</td>
<td>Is opioid dose related to survival in last 2 d of life?</td>
<td>Secondary analysis of a prospective observational study</td>
<td>209 patients (172 on opioids) with mixed cancers on a palliative care unit in Japan</td>
</tr>
<tr>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
<td>Confounders/limitations</td>
</tr>
<tr>
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<tr>
<td>High-dose opioids (299-599 mg/d OME): 19 patients (4%). Very high-dose opioids (&gt;599 mg/d OME): 36 patients (8%)</td>
<td>Low-dose opioids (&lt;299 mg/d OME): 398 patients (88%)</td>
<td>No statistical difference in survival time between opioid doses. Mean survival time: very high dose 13 d; high dose 15 d; low dose 14 d</td>
<td>Retrospective; mixed cancers; opioids pooled; short-term follow-up—from hospice admission; small number of patients on high doses</td>
</tr>
<tr>
<td>Marked increase in opioid dose at the end of life; 28 patients (12%)</td>
<td>No/small increase in opioid dose at the end of life; 210 patients (88%)</td>
<td>No statistical difference in survival from hospice admission. Mean survival: 21 d for dose increase group vs 16 d for no/small increase group ($P = 0.7$)</td>
<td>Retrospective; mixed cancers; opioids pooled; small increase in the median daily opioid dose in the last week of life. Small numbers in dose increase group</td>
</tr>
<tr>
<td>High-dose opioids (&gt;240 mg OME/48 h): 45 patients (22%)</td>
<td>No opioids or low-dose opioids (&lt;240 mg OME/48 h): 164 patients (78%)</td>
<td>No difference in survival time between opioid doses ($P = 0.23$)</td>
<td>Mixed cancers; opioids pooled; short-term follow-up. Small numbers of patients in higher dose opioid groups. Opioids only recorded in last 2 d of life</td>
</tr>
</tbody>
</table>
EOL Studies - Effect of opioids on survival

- 5 indicated a potential association of increased survival with higher doses of opioids or increases in opioid dose in the last days of life
- 5 reported no relationship between survival and overall dose or change in opioid dose
- 3 reported higher opioid dose or increasing doses of opioids associated with a shorter survival
Portenoy et al.

Best quality EOL study - secondary data analysis

- IVME >20 mg/d equally associated with a shorter survival compared with ≤17 mg/d
- Mean survival
  - 27 d for patients on ≤17 mg/d IVME vs. 12 d for patients on 20-25 mg/d IVME
- Opioid dose accounted for 6%-8% of the overall effect on survival (depending on the analysis)
Studies in patients with a longer prognosis (months to years)

- 7 studies
- GRADE criteria: 3 studies were moderate, 3 were low and 1 was very low quality
- 3 RCTs, 3 prospective studies, and 1 retrospective study
- Mean sample size was 485 patients
<table>
<thead>
<tr>
<th>Study</th>
<th>Topic</th>
<th>Study Design</th>
<th>Participant Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skipworth et al.(^{67}); interaction of gonadal status with systemic inflammation and opioid use in determining nutritional status and prognosis in advanced pancreatic cancer</td>
<td>Investigation into the interaction of gonadal status with systemic inflammation and opioids in determining nutritional status and prognosis in advanced pancreatic cancer</td>
<td>A multicentre RCT</td>
<td>167 patients (from 175 randomised) with advanced pancreatic cancer; 43; on opioids, in the USA</td>
</tr>
<tr>
<td>Zylla et al.(^{80}); opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer</td>
<td>What is the association of opioid dose on cancer; progression and survival in patients with metastatic prostate cancer?</td>
<td>Retrospective observation cohort analysis</td>
<td>593 patients with stage IV prostate cancer; in the USA (test cohort—113 from Minneapolis VA tumour registry; validation cohort—480 patients from VA Central Cancer Registry)</td>
</tr>
<tr>
<td>Halabi et al.(^{38}); updated prognostic model for predicting overall survival; in first-line chemotherapy for patients with metastatic; castration-resistant prostate cancer</td>
<td>To develop a model for predicting survival; in chemotherapy for patients with metastatic; castration-resistant prostate cancer</td>
<td>Data from 2 phase III RCTs (1050 + 942 patients)</td>
<td>1992 patients with metastatic castration-resistant prostate cancer—data were split into training, testing, and validation sets</td>
</tr>
</tbody>
</table>
Patients on opioids: median OME dose for females 40 mg and for males 80 mg; 25 male (15%); 18 female (11%)

Patients not on opioids: 65 male (39%); 59 female (35%)

Survival was shorter in male patients using opioid compared with nonopioid-users; median 78 d vs 132 d (P = 0.009)

Opioids pooled; small numbers of patients when subdivided into sex

Average opioid dose (OME) for 1 y before diagnosis and from diagnosis to death/last follow-up

Compared with other opioid doses

Increased opioid requirement was associated with shorter survival (P < 0.001)

Retrospective; opioids pooled

Patients on opioids: 521 patients (29%)

Patients not on opioids: 1249 patients (71%)

Opioid use was associated with a shorter survival (Hazard Ratio 1.09)

Secondary data analysis. Data for a specific patient group did not check dose effect
Longer prognosis studies - Effect of opioids on survival

• 6/7 studies (3 RCTs, 2 of the 3 prospective studies and the retrospective study) described a potential association between strong systemic opioid use or increasing dose and shorter survival.

• Did not have survival as a primary, appropriately powered, endpoint

• Differences between opioids not determined

• Plus....
Limitations of the included studies

• **P** - mostly mixed cancers
  – Some studies used discrete population with a very limited life expectancy such as hospice admission.

• **I** - The starting point for opioid use, the duration of opioid administration, or when data were recorded differed between studies.

• **C** - the control groups were not directly matched (ie, not patients who had refractory severe symptoms but did not choose opioids).

• **O** - The time point from which survival was measured varied
Also...

Greater analgesic requirements and shorter survival is likely to be mediated by painful progressive cancer...
Opioids and infection

Evidence that certain opioids can suppress the anti-infection arm of the immune system and could increase the risk of infection

(Dublin et al., 2011).
Opioids and infection

• Correlation between the administration of morphine or oxycodone and the development of infections in patients with cancer pain

• Retrospective

• More patients treated with morphine developed infections than those patients treated with oxycodone (odds ratio = 3.6)

(Suzuki et al., 2013).
Chronic Non-Cancer Pain

- Retrospective cohort study in Tennessee
  - not palliative or end-of-life care
- 22,912 new long-acting opioids and controls
  - analgesic anticonvulsants/TCAs
- HR 1.64 all-cause mortality
- HR 1.90 out-of-hospital deaths
- HR 4.16 first 30 days of treatment

Ray, JAMA, 2016
Chronic Non-Cancer Pain - methadone

• Retrospective cohort study in Tennessee
  – not palliative or end-of-life care
• 32,742 morphine SR (90 mg/d); 6014 methadone (40 mg/d)
• Methadone had a 46% increased risk of death; HR 1.46
• ≤20 mg/d methadone associated with an increased risk of death (HR 1.59) relative to <60 mg/d morphine

Ray, JAMA int med, 2015
Non-cancer: COPD

- Retrospective population-based cohort study
- COPD patients prescribed opioids are more likely to:
  - Attend ED
  - Have pneumonia
  - Die within 30 days of starting opioids
    - COPD or pneumonia-related mortality (HR 2.16, p<0.0001)
    - All-cause mortality (HR 1.76, p<0.0001)
- Association (not causation)
  - ?worsening illness necessitating opioids

Vozoris et al, 2016
COPD

• Population based cohort study in Sweden
• 2249 patients starting LTOT for COPD
• Dose response relationship of opioids with mortality
  – ≤30 mg OME/d not associated with increased mortality

Ekström et al, 2014
HIV

• Prospective study of HIV-infected patients receiving ART and matched uninfected patients
• 16,989 HIV-infected and 47,613 uninfected
• Long-term opioids associated with an increased risk of death
  – HR 1.46 HIV-infected patients
  – HR 1.25 uninfected patients
  – Especially ≥50 mg OME/d

Weisberg et al, 2015
Cancer surgery
Opioids – silent killers?

Some opioids have been associated with decreased survival in different groups

Mostly retrospective studies
Is there a not so silent killer?
Cancer pain

- Cancer
- Opioids
- Immune system
- Pain
Opioid-induced immunomodulation - in patients at risk of cancer/infection

Boland et al, BJC 2014
Implications for patients

- Not important in `end of life` care
- Further research with clinical outcomes in patients with a good prognosis

Good pain control is vital
- Multimodal analgesia
  - Optimise non-pharmacological interventions
  - Other interventions
  - Optimise non-opioid analgesia
  - Lower doses of opioids
- Less toxic opioids/route???
Thank you - Questions?

Class 0: things I believe

Class 0a: things I believe despite the available data

Class 1: randomized, controlled clinical trials (RCCTs) that agree with what I believe

Class 2: other prospectively collected data

Class 3: expert opinion

Class 4: RCCTs that don't agree with what I believe

Class 5: what you believe that I don't