Opioid adverse reactions – not the “usual suspects”!

DR ANDREW DAVIES
Overview

- Introduction
- Musical hallucinations
- Charles Bonnet syndrome
- (Nightmares, vivid dreams)
- Sleep disordered breathing
- Sphincter of Oddi dysfunction
- Conclusion
Introduction
Introduction

An adverse reaction to a drug has been defined as any noxious or unintended reaction to a drug that is administered in standard doses by the proper route for the purpose of prophylaxis, diagnosis, or treatment”.

Vervloet & Durham, 1998
# Introduction

## Classification of adverse reactions to drugs

<table>
<thead>
<tr>
<th>Reactions that may occur in anyone:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug overdose - Toxic reactions linked to excess dose or impaired excretion, or to both</td>
</tr>
<tr>
<td>• Drug side effect - Undesirable pharmacological effect at recommended doses</td>
</tr>
<tr>
<td>• Drug interaction - Action of a drug on the effectiveness or toxicity of another drug</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reactions that occur only in susceptible subjects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug intolerance - A low threshold to the normal pharmacological action of a drug</td>
</tr>
<tr>
<td>• Drug idiosyncrasy - A genetically determined, qualitatively abnormal reaction to a drug related to a metabolic or enzyme deficiency</td>
</tr>
<tr>
<td>• Drug allergy - An immunologically mediated reaction, characterised by specificity, transferability by antibodies or lymphocytes, and recurrence on re-exposure</td>
</tr>
<tr>
<td>• Pseudoallergic reaction - A reaction with the same clinical manifestations as an allergic reaction (eg, as a result of histamine release) but lacking immunological specificity</td>
</tr>
</tbody>
</table>
Introduction
Introduction

Anti-diarrhoeal  Constipation
“Although opioid-related adverse events are an important issue when treating cancer-related pain, realistic rates of adverse events per type of opioid are unknown because of immense heterogeneity and lack of systematic assessment and reporting”.

Oosten et al, 2015
Introduction
Introduction
Introduction

Prevalence xerostomia – 16%
(case note review)

Potter, 2003

Prevalence xerostomia – 78-82%
(research studies – MSAS used)

Shorthose & Davies, 2003
Introduction
Introduction
Musical hallucinations
Hallucinations

Opioids can (often) cause visual hallucinations – Odds Ratio of 4.48 for hospice inpatients

Fountain, 2001

Opioids can (sometimes) cause auditory hallucinations

Opioids can (rarely) cause tactile hallucinations
Musical hallucinations

Epidemiology:
Prevalence unknown
(AD – 2 cases)
More common in elderly / females

Aetiology:
Pathophysiology unknown
(Peripheral mechanism; central mechanism)
Musical hallucinations

Aetiology:
Hearing impairment (acquired)
Psychiatric disease, e.g. depression
Neurological disease, e.g. cerebral atrophy
Systemic disease, e.g. Lyme disease
Drug treatment, e.g. ketamine
Musical hallucinations

Clinical features:
Sound appears external
Sound lateralises both ears

Single tune / medley of tunes
Songs / instrumentals / bird songs
Familiar / non-contemporary / tuneful
[Childhood, religious, patriotic, operatic]
Musical hallucinations

Clinical features:
No features of psychosis
No features of opioid toxicity
Musical hallucinations

Management:
Reassurance
Antipsychotic drugs
Opioid discontinuation
Opioid switching
Who is this?
Charles Bonnet syndrome

Analogous syndrome in patients with visual impairment

2 (3) case reports of worsening symptoms in patients receiving opioid analgesics
(Nightmares, vivid dreams)
Nightmares / vivid dreams

Nightmares / vivid dreams

Opioids do not cause nightmares / vivid dreams

Sleep disturbance is associated with nightmares / vivid dreams

Physical burden is associated with nightmares / vivid dreams

Psychological burden is associated with nightmares / vivid dreams
Sleep disordered breathing
Sleep disordered breathing

“it is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally only occurs in the opioid-naïve patient and is antagonised by pain”

Sleep disordered breathing

“Prescription of long-acting opioids for chronic noncancer pain, compared with anticonvulsants or cyclic antidepressants, was associated with a significantly increased risk of all-cause mortality, including deaths from causes other than overdose, with a modest absolute risk difference”

Ray et al, 2016
Sleep disordered breathing

Table 3. Mortality According to Underlying Cause of Death

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Anticonvulsant or Cyclic Antidepressant (Person-Years of Follow-up = 8066)</th>
<th>Long-Acting Opioid (Person-Years of Follow-up = 11 070)</th>
<th>Adjusted Hazard Ratio (95% CI)(^a)</th>
<th>Adjusted Risk Difference (95% CI)(^ab)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>87 107.9</td>
<td>185 167.1</td>
<td>1.64 (1.26 to 2.12)</td>
<td>68.5 (28.2 to 120.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Out-of-hospital</td>
<td>60 74.4</td>
<td>154 139.1</td>
<td>1.90 (1.40 to 2.58)</td>
<td>67.1 (30.1 to 117.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unintentional overdose(^c)</td>
<td>7 8.7</td>
<td>34 30.7</td>
<td>3.37 (1.47 to 7.70)</td>
<td>20.6 (4.1 to 58.1)</td>
<td>.004</td>
</tr>
<tr>
<td>Other causes</td>
<td>53 65.7</td>
<td>120 108.4</td>
<td>1.72 (1.24 to 2.39)</td>
<td>47.4 (15.7 to 91.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>36 44.6</td>
<td>79 71.4</td>
<td>1.65 (1.10 to 2.46)</td>
<td>28.9 (4.6 to 65.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3 3.7</td>
<td>10 9.0</td>
<td>3.00 (0.81 to 11.09)</td>
<td>7.4 (−0.7 to 37.5)</td>
<td>.10</td>
</tr>
<tr>
<td>Other injury</td>
<td>11 13.6</td>
<td>19 17.2</td>
<td>1.15 (0.54 to 2.47)</td>
<td>2.1 (−6.3 to 20.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Other</td>
<td>3 3.7</td>
<td>12 10.8</td>
<td>3.72 (1.04 to 13.30)</td>
<td>10.1 (0.2 to 45.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Hospital</td>
<td>27 33.5</td>
<td>31 28.0</td>
<td>1.00 (0.59 to 1.69)</td>
<td>0 (−13.6 to 23.1)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for baseline propensity score decile, age, and calendar year during follow-up.

\(^b\) Risk differences for the specific causes of death do not sum because the regression model parameters are estimated separately for each cause.

\(^c\) The cohort excluded patients with a diagnosis of or procedure for treatment of substance abuse other than nicotine or alcohol as well as those prescribed buprenorphine. Because such patients would plausibly have increased risk of overdose, overdose mortality in the study cohort is likely to be lower than that in a more general patient population.
Sleep disordered breathing

“...adequate breathing during wakefulness does not provide any assurance that it will be adequate during sleep”.

*Hillman, 2015*

“...sleep and opioids reduce respiratory drive, as shown by decreased ventilatory response to hypoxia and hypercapnia”.

*Correa et al, 2015*
Sleep disordered breathing

“There is persuasive evidence that SDB (OSA, CSA and mixed OSA and CSA) is common in patients receiving COT and that there is a strong relationship between SDB and risk of unintentional opioid related mortality and morbidity”.

_Cheatle et al, 2015_

SDB – sleep disordered breathing
OSA – obstructive sleep apnoea
CSA – central sleep apnoea
COT – chronic opioid therapy.
Sleep disordered breathing

Prevalence (all types):
- 70% (42-85%)
- (Moderate severity)
Sleep disordered breathing

Opioid-related sleep disordered breathing:
- Central sleep apnoea
- Obstructive sleep apnoea
- Hypopnoeas
- Hypoxaemia
- Ataxic or irregular breathing patterns
  - ataxic breathing
  - Biot respiration
  - Cheyne Stokes respiration
## Sleep disordered breathing

<table>
<thead>
<tr>
<th>Condition</th>
<th>Airflow</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>![Normal airflow graph]</td>
<td></td>
</tr>
<tr>
<td>OSA</td>
<td>![OSA airflow graph]</td>
<td>Excursions of the diaphragm</td>
</tr>
<tr>
<td>Central sleep apnea</td>
<td>![Central sleep apnea airflow graph]</td>
<td>Oxygen saturation (arterial)</td>
</tr>
<tr>
<td>Ataxic breathing</td>
<td>![Ataxic breathing airflow graph]</td>
<td></td>
</tr>
<tr>
<td>Biot respiration</td>
<td>![Biot respiration airflow graph]</td>
<td></td>
</tr>
<tr>
<td>Cheyne-Stokes respiration</td>
<td>![Cheyne-Stokes respiration airflow graph]</td>
<td></td>
</tr>
</tbody>
</table>

*Figure 1 – Abnormal patterns of breathing associated with opioid use.*
Sleep disordered breathing

Risk factors (general):
- Type of opioid - methadone
- Dose of opioid - > 200 mg MED
- Concomitant use benzodiazepines
- Concomitant use hypnotics
Sleep disordered breathing

Central sleep apnoea:
- 24% (14-60%)
- More common (than obstructive sleep apnoea)
- Cessations in airflow in the absence of the usual corresponding respiratory effort
- Depression of hypoxic and hypercapnic ventilatory drives (especially hypercapnic ventilatory drive)
Sleep disordered breathing

Risk factors (CSA):
- Age - > 65yr
- Male gender
- Stroke
- Brain tumour
- Heart disorders
Sleep disordered breathing

Obstructive sleep apnoea:
- Cessations in airflow in the presence of the usual corresponding respiratory effort
- ? Reduction in airway muscle activation
Sleep disordered breathing

Risk factors (OSA):
- Age -> 65yr
- Male gender
- Family history
- BMI
- Neck circumference
- Smoking
- Nasal congestion
- “Narrowed pathway”
Sleep disordered breathing

Management:
- Reduce opioid dose
- Address risk factors
- Referral sleep service
  - continuous positive airway pressure (CPAP)
  - bilevel positive airway pressure ventilation (BPAP)
  - automatic self-adjusting positive airway pressure (APAP)
  - servo-controlled ventilation (ASV or BPAP adapt)
Sphincter of Oddi dysfunction
Sphincter of Oddi:

- Hepatopancreatic sphincter
- Glisson's sphincter

- Facilitates filling of the gallbladder
- Regulates flow of bile and pancreatic secretions into the duodenum
- Prevents reflux from the duodenum
Sphincter of Oddi
Sphincter of Oddi dysfunction

Epidemiology:
- Prevalence ~ 1.5-2.2%
- Female > male (Odds Ratio 3.3)
Sphincter of Oddi dysfunction

Pathophysiology:
- Stenosis
- Spasm (muscle)
- Combination

Aetiology:
- Post cholecystectomy (biliary*)
- Opioids
Sphincter of Oddi dysfunction

Clinical features:
- Chronic recurrent biliary pain (↑ transaminases)
- Chronic recurrent idiopathic pancreatitis (↑ amylase)
- Combination
Sphincter of Oddi dysfunction

Diagnosis:
- Rome IV criteria
- [Milwaukee classification]
Sphincter of Oddi dysfunction

Investigations:
- Biliary manometry
- Other (less invasive) investigations
Sphincter of Oddi dysfunction

Management (general):

- Pharmacological – nifedipine, GTN, hyoscine butylbromide, phosphodiesterase type 5 inhibitor, tricyclic antidepressants, somatostatin analogues, botulinum toxin

- Endoscopic – sphincterotomy

- Surgical – sphincteroplasty
Sphincter of Oddi dysfunction

Management (opioid-related):

- Avoidance opioids
- “Good” opioids - buprenorphine, pethidine, tramadol
- “Bad” opioids - codeine, fentanyl, morphine, (oxycodone), tapentadol, loperamide
- Use of antispasmodics – lack of evidence
- Use of PAMORAs – “emerging” evidence
Conclusion
Conclusion

I think you have “medication overuse headache” from taking codeine for your migraine.
Conclusion

Message to non-specialists:

Opioids are not the cause of every problem!
Conclusion

Message to specialists:

Opioids can be the cause of many problems

(so it could be the opioid!)