Role of pregabalin and gabapentin in drug related deaths

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Pregabalin and gabapentin community prescriptions (England)

Epilepsy, Pain, Anxiety (pregabalin)

- Insomnia, migraine, mania, bipolar disorder and alcohol withdrawal (gabapentin)
Pregabalin and gabapentin community prescriptions (England)


Abuse
- relaxation
- enhanced sociability
- euphoria
- dissociation
- sedation

(gabapentin)
Acute deaths involving gabapentin and pregabalin (England & Wales)
Acute deaths involving gabapentin and pregabalin (England & Wales)

<table>
<thead>
<tr>
<th>Year</th>
<th>Gabapentin NRS</th>
<th>Gabapentin ONS</th>
<th>Pregabalin NRS</th>
<th>Pregabalin ONS</th>
</tr>
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<tbody>
<tr>
<td>2016</td>
<td>154</td>
<td>59</td>
<td>71</td>
<td>111</td>
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Graph showing the number of deaths mentioning a gabapentoid from 2004 to 2016.
Deaths also involving opioids (England & Wales)

Opioids were involved in >80% of gabapentoid deaths (90% in 2016)
Deaths also involving opioids (England & Wales)

Is the presence of both just because heroin addicts like gabapentoids or is there an interaction?
Interviews with active heroin users in Bristol
- attending Bristol Drugs Project Needle Exchange
- screened for known opioid users
- £10 fee on completion of interview

Areas discussed
- Perceived protection
  - from on top heroin use on methadone or Subutex OST

- Benefits and hazards of also using non-opioid drugs
  - alcohol
  - cocaine
  - benzodiazepines
  - gabapentin and pregabalin
Interviewed 30 users

- 19 males and 11 females

- different lengths of opioid use
  20 long term (>10 years)
  4 medium term (5 – 10 years)
  6 short term (<5 years)

- different styles of use (smoking and injecting)

- different opioid substitution treatments
Use of gabapentoids

- 21 of 30 had used gabapentoids
- most (19 of 21) used pregabalin
  - 3 were daily users
  - 3 used it weekly
  - 5 used it intermittently
  - for 10 it was just a one-off occasion

Street purchase mainly
- 2 obtained it from friends who were prescribed it
- 3 were prescribed pregabalin for chronic pain

Taken orally some time prior to heroin injection
Doses varied – 250mg tablet to 1500mg taken orally as tablets
Perceived effects of gabapentoids

- give a buzz on their own (feeling of being drunk)
- enhance the effect of the heroin
- caused blackouts and loss of control (zombies)
- increased the risk of overdose
- helps to cope with withdrawal between heroin doses
- reduced craving for heroin
Preclinical studies of pregabalin

- Does pregabalin depress respiration?
- If so is it additive with opioids?
- Does pregabalin alter opioid tolerance?
Monitoring mouse respiration

Air + 5% CO₂ Canister

Gas flow regulator

Transducer

Plethysmograph Chamber

EMKA Software

Extractor Pump
Pregabalin and morphine additively depress respiration.
Low dose pregabalin reverses morphine tolerance

- **Pregabalin 20 mg/kg**
- **Morphine 10 mg/kg**

6 day morphine treatment | respiration

- **Naive**
- **Morphine pretreated**
- **Morphine pretreated + pregabalin + morphine challenge**
Pregabalin – opioid interaction

**Acute**
- pregabalin (*high dose*) additive with morphine, methadone, fentanyl, oxycodone

**Tolerance**
- pregabalin (*low dose*) reverses morphine tolerance, oxycodone tolerance
  
  **BUT NOT**
  methadone tolerance
Drug specific mechanisms of opioid tolerance

- Methadone
  - GRK2/3
  - arrestin
- Morphine
  - PKC_{\alpha,\gamma}

Methadone
Fentanyl

Morphine
Heroin
6-MAM
Oxycodone
Agonist specific mechanisms of opioid tolerance

Methadone
Fentanyl

Morphine
Heroin
6-MAM
Oxycodone

PKC<sub>α,γ</sub>
GRK2/3
arrestin

Alcohol
Tamoxifen
Pregabalin
Diversion of gabapentoid prescription

- Need for greater awareness amongst GPs
- Need for alternative treatments for chronic pain
HM Prison Service (South West of England)
Dr Catherine Glover, Medical Director

THE FACTS
GABAPENTIN
PREGABALIN

WHAT ARE PREGABALIN AND GABAPENTIN?
They were originally used to treat epilepsy. They are also licenced to treat nerve pain and some types of anxiety.

WHY DO WE WORRY ABOUT IT?
- Use of these drugs can lead to dependence.
- Pregabalin and Gabapentin can cause drowsiness, sedation, slow down breathing, and in extreme cases death.
- There are particular issues in secure settings where deaths have been found to involve illicit and/or diverted medication.

WHAT TO BE AWARE OF...
- Deaths involving Pregabalin or Gabapentin have increased drastically in the last 5 years. 78% of these are associated with opiate use.
- Opiates & Pregabalin together slow down breathing further. Naloxone does not reverse respiratory depression caused by Pregabalin/Gabapentin.

WHAT USERS ARE SAYING:
- “There is more chance for overdose if you take heroin and Pregabalin together because Pregabalin takes, like, two/three hours to kick in. So, like, and then we think ‘argh it hasn’t kicked in, oh I’ll have a dig’, so we have a dig and then that kicks in, and then there’s more chance of you going over.”
- “They’re like zombies; they don’t know what they’re doing... Pregabalin does make people feel like a zombie.”
- “Don’t like ’em... I woke up just feeling like jelly, didn’t know what happened.”
- “That’s one of my last overdoses. I knew the heroin was strong and I didn’t know, I was naive.”

REMEMBER THE S.M. SERVICE IS HERE TO HELP

University of BRISTOL
5% increase in overdose deaths per 100,000 increase in prescriptions