Addictions Webinar Series: Dependence on opioid drugs and prescription medication – an update for psychiatrists

Addictions Webinar Series

Dependence on benzodiazepines, “z” drugs and gabapentenoids
Wednesday 27.10.21

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Northern Health and Social Care Trust
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Outline of presentation

- Review risks vs meaningful benefits within psychiatric practice
  - Benzodiazepines
  - “Z” Drug
  - Gabapentinoids (focus on pregabalin)
- Discuss strategies to assist withdrawal from these medications
- Raise awareness of the role of these drugs in drug related deaths and how this should influence our prescribing practice
Declaration of interests

• Nil
• Public Health England Dependence and withdrawal associated with some prescribed medicines An evidence review (2019)
• benzodiazepines
• z-drugs
• gabapentin and pregabalin
• opioids for chronic non-cancer pain
• antidepressants
Safety in pregnancy

Benzodiazepines
“If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.”

SmPC Diazepam
https://www.medicines.org.uk/emc/product/4523/smpc
(accessed online 24.10.21)

Gabapentenoids
“pregabalin may be associated with a slightly increased risk of major congenital malformations but further data are needed to reach a definitive conclusion;”
MHRA Antiepileptic drugs: review of safety of use during pregnancy Published 7 January 2021

“Pregnant women who take pregabalin are recommended to take a higher dose of folic acid. Your doctor might prescribe a high dose of folic acid (5mg a day) for you to take during the first 12 weeks of pregnancy.”
Pregabalin: medicine to treat epilepsy and anxiety - NHS (www.nhs.uk)
(accessed 16.10.21)
Clinical indications for benzodiazepines

- Hypnotic
- Anxiolytic
- Muscle relaxant
- Anticonvulsant
- Assisted withdrawal from alcohol and other drugs
- Some role in anaesthetics

- Short term use “rapid tranquilisation” in excitement, agitation or severe psychotic symptoms
- Diazepam licensed for short term use (2-4 weeks) for disabling anxiety
Risks or harms associated with benzodiazepines

- Cognitive impairment
- Psychomotor risks (falls, particularly in older people, ↑ risk RTAs
- Tolerance,
  - more pronounced for the anticonvulsant and sedative effects.
  - tolerance to the hypnotic and anxiolytic effects can also develop, but probably less often and more slowly. (Baldwin 2013)
- Dependence - emergence of withdrawal symptoms on either stopping or too rapidly reducing treatment.
- Problem drug use/ addiction
NICE Clinical Knowledge Summary (CKS)
Benzodiazepine and z-drug withdrawal: Diazepam (Last revised in January 2019)

- Contraindications and cautions
- Adverse effects
- Drug interactions
- Switching to diazepam
- Links to The Ashton Manual: Benzodiazepines: how they work and how to withdraw Revised 2002

https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/prescribing-information/diazepam/#switching-to-diazepam
(accessed 23.10.21)
Management of benzodiazepine misuse and dependence

• “The management of dependence involves either gradual benzodiazepine withdrawal or maintenance treatment. Prescribing interventions, substitution, psychotherapies and pharmacotherapies can all contribute.

• Unless the patient is elderly, it is helpful to switch to a long-acting benzodiazepine in both withdrawal and maintenance therapy. The dose should be gradually reduced over weeks to lower the risk of seizures.

• Harms from drugs such as zopiclone and zolpidem are less well characterized. Dependence is managed in the same manner as benzodiazepine dependence.”
### Table 4. Acute withdrawal symptoms

<table>
<thead>
<tr>
<th>Anxiety symptoms</th>
<th>Distorted perceptions</th>
<th>Major incidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>Distorted perceptions</td>
<td>Mainly when high doses are stopped abruptly</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Agitation</td>
<td>Fits (1–2% of patients)</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>Tremor</td>
<td>Delirium (rare)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Headache</td>
<td>Transient hallucinations (visual, tactile, auditory) or illusions (rare)</td>
</tr>
<tr>
<td>Poor memory</td>
<td>Weakness</td>
<td>Psychosis (very rare)</td>
</tr>
<tr>
<td>Depression</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Paranoia</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Intrusive memories</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Cravings</td>
<td>Diarrhoea</td>
<td></td>
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<tr>
<td>Nightmares</td>
<td>Constipation</td>
<td></td>
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<tr>
<td>Excitability</td>
<td>Palpitations</td>
<td></td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>Rashes</td>
<td></td>
</tr>
<tr>
<td>Social phobia</td>
<td>Tingling, numbness, altered sensation</td>
<td></td>
</tr>
<tr>
<td>Obsessions</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Rage, aggression</td>
<td>Flu-like symptoms</td>
<td></td>
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<tr>
<td>Irritability</td>
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</tr>
</tbody>
</table>
Options for tapering benzodiazepines

• Direct taper
• Direct taper, then later switch to equivalent dose of diazepam
• Switch to equivalent dose diazepam from outset before reduction (consider cross taper if switching lorazepam to diazepam)
• “Gradual dose tapering, such as 5–10% reduction every 1–2 weeks, or an eighth of the dose fortnightly, with a slower reduction at lower doses, and titrated according to the severity of withdrawal symptoms.” (NICE CKS Benzodiazepine and z-drug withdrawal: Last review Jan 2019)
### Equivalent doses of oral benzodiazepines

Specialist Pharmacy Service 06.07.21
Gillian Lewis

(Must also consider half life, metabolism, co-existing morbidities)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>250 micrograms</td>
<td>250 micrograms</td>
<td></td>
<td>500 micrograms (250 – 500 micrograms)</td>
<td>250 micrograms</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>12.5mg</td>
<td>12.5mg</td>
<td>12.5mg</td>
<td>12.5mg (10 – 25mg)</td>
<td>12.5 – 15mg</td>
</tr>
<tr>
<td>Clobazam</td>
<td>10mg</td>
<td>10mg</td>
<td></td>
<td>10mg</td>
<td>10mg</td>
</tr>
<tr>
<td>Clonazepam*</td>
<td>250 micrograms</td>
<td>250 micrograms</td>
<td></td>
<td>250 micrograms (0.25 – 4mg)</td>
<td>250 micrograms</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>7.5 – 15mg</td>
<td>7.5 – 15mg</td>
<td></td>
<td>7.5 – 15mg</td>
<td>7.5 – 15mg</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>0.5 – 1mg</td>
<td>0.5 – 1mg</td>
<td></td>
<td>0.5 – 1mg</td>
<td>0.5 – 1mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>500 micrograms</td>
<td>500 micrograms</td>
<td></td>
<td>500 micrograms</td>
<td>500 micrograms</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>0.5 – 1mg</td>
<td>0.5 – 1mg</td>
<td>0.5 – 1mg</td>
<td>0.5 – 1mg</td>
<td>0.5 – 1mg</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg (2.5 – 20mg)</td>
<td>5mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg (10 – 20mg)</td>
<td>10 – 15mg</td>
</tr>
<tr>
<td>Temazepam</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
</tr>
</tbody>
</table>
Benzodiazepine equivalent doses of “Z” drugs

Zolpidem
- 10mg zolpidem equivalent to 5mg diazepam (CKS 2019)
- The elimination half-life is short, with a mean of 2.4 hours (0.7-3.5) and a duration of action of up to 6 hours. (SmPC)

Zopiclone
- 7.5 mg Zopiclone equivalent to 5mg diazepam (CKS 2019)
- The elimination half-life is approximately 5 hours (SmPC).

https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/prescribing-information/diazepam/
Lack of convincing evidence for medications to assist withdrawal from benzodiazepines (Cochrane Database 2018)

“We are uncertain whether valproate and tricyclic antidepressants increase the chance of discontinuing benzodiazepines, and whether benzodiazepine withdrawal symptoms are reduced by pregabalin, captodiame, paroxetine, tricyclic antidepressants, and flumazenil, as we assessed the quality of the evidence as very low.

We are uncertain as to whether symptoms of anxiety and withdrawal of benzodiazepines are reduced by carbamazepine, pregabalin, captodiame, paroxetine, and flumazenil, as we assessed the quality of the evidence as very low.”


https://doi.org/10.1002/14651858.CD011481.pub2
Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression - MHRA/CHM advice (March 2020)

- Benzodiazepines and benzodiazepine-like drugs co-prescribed with opioids can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.
- Only co-prescribe if there is no alternative and, if necessary, the lowest possible doses should be given for the shortest duration.
- Inform patients of risk respiratory depression and sedation, and get urgent medical attention should these occur.
Benzodiazepines: Risks and benefits. A reconsideration

David S Baldwin¹, Katherine Aitchison², Alan Bateson³, H Valerie Curran⁴, Simon Davies⁵, Brian Leonard⁶, David J Nutt⁷, David N Stephens⁸ and Sue Wilson⁷

Abstract
Over the last decade there have been further developments in our knowledge of the risks and benefits of benzodiazepines, and of the risks and benefits of alternatives to benzodiazepines. Representatives drawn from the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists and the British Association for Psychopharmacology together examined these developments, and have provided this joint statement with recommendations for clinical practice. The working group was mindful of widespread concerns about benzodiazepines and related anxiolytic and hypnotic drugs. The group believes that whenever benzodiazepines are prescribed, the potential for dependence or other harmful effects must be considered. However, the group also believes that the risks of dependence associated with long-term use should be balanced against the benefits that in many cases follow from the short or intermittent use of benzodiazepines and the risk of the underlying conditions for which treatment is being provided.
Editorial: Benzodiazepines: it's time to return to the evidence

Silberman E, Balon R, Starcevic V et al.
• Broadcast May 26 2021

Maudsley Webinar Series

BRAINCAST continues with Pospo and Professor Edward K. Silberman, on Benzodiazepines

https://youtu.be/ClSdj4CiZ8w
Section on benzodiazepines (pages 119-123)

- Used in high dose with other sedatives or stimulants – refer to addiction services
- “there is evidence that long-term prescribing (especially of more than 30mg diazepam equivalent per day) may cause harm”.
Maintenance prescribing of benzodiazepines for benzodiazepine use disorders

- Benzodiazepines most closely linked to drug deaths in Scotland are Etizolam (6-10 times more potent than diazepam) and Alprazolam.
- Prescribing diazepam may reduce use of more dangerous benzodiazepines.
  - Scottish Drug Death Task Force have produced a MAT Standards Informed Response for Benzodiazepine Harm Reduction.
Drug related deaths in Scotland 2020 National Records of Scotland (2021)

Figure 7B: Number of drug-related deaths in Scotland: in total, and for which certain benzodiazepines were implicated in the cause of death
ACMD advice on the control of Z-drugs (zaleplon, zolpidem and zopiclone) (2013)

- One report suggested risk of abuse one third of benzodiazepines
- Zopiclone withdrawal - Anxiety • Tachycardia • Tremor • Sweating • Rebound insomnia • Flushes and palpitations • Derealisation and • Convulsions
- Role in drug related death was difficult to interpret
“Risks associated with the long-term use of benzodiazepine and 'Z drug' hypnotic drugs have been well recognised for many years. These risks include falls, accidents, cognitive impairment, dependence and withdrawal symptoms, and an increased risk of dementia.”

Melatonin also associated with falls.
NICE Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia
Technology appraisal guidance [TA77]Published: 28 April 2004

- “..estimated that 10–30% of chronic benzodiazepines users are physically dependent on them and 50% of all users suffer withdrawal symptoms”
- “…no compelling evidence of a clinically useful difference between the Z-drugs and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse.”
Withdrawal from zopiclone 7.5 mg per day or less:

Reduce the daily dose by half of a 3.75 mg tablet (1.875 mg) every 2 weeks.
The target dose for when to stop is when the person is taking only half of a 3.75 mg tablet.

If stopping is not possible at the target dose, one option is to convert to diazepam to complete the withdrawal, although this is controversial. Estimated total withdrawal time: 16–20 weeks or longer.

(NICE CKS 2019)
Gabapentenoids

**Pregabalin is licensed for:**
- Epilepsy
- Neuropathic pain
- Generalised anxiety disorder - supported by NICE

**Gabapentin is licensed for:**
- Epilepsy
- Peripheral neuropathic pain
Over 7,000,000 prescription items for both Pregabalin and Gabapentin were dispensed in England in 2019.

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Prescription items dispensed in the community in England in 2019*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>2,274,769</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>7,296,052</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2,965,550</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>2,402,526</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>109,137</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>188,342</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>675,597</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>7,398,604</td>
</tr>
<tr>
<td>Topiramate</td>
<td>967,305</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>164,243</td>
</tr>
</tbody>
</table>

MHRA
Antiepileptic drugs: review of safety of use during pregnancy
7 January 2021


Published 7 January 2021
Prescribe pregabalin with caution to people:

- At risk of **cardiovascular compromise** — due to the risk of congestive heart failure
- At risk of **suicide** - there is a small increased risk of suicidal ideation and behaviour in people treated with antiepileptic drugs.
- Using medications that can cause **constipation** (such as opioids). During combination therapy, measures to prevent constipation should be considered, especially in women and older people.
Contraindications and cautions of pregabalin (1)
https://cks.nice.org.uk/topics/generalized-anxiety-disorder/prescribing-information/pregabalin
(last revised Feb 2021)

Prescribe pregabalin with caution to people:

- With renal impairment
- At risk of encephalopathy — cases of encephalopathy have been reported, mostly in people with underlying conditions that may precipitate the condition.
- With diabetes — pregabalin may cause weight gain.
- At risk of falls (such as older people) — pregabalin has been associated with dizziness and somnolence, and there have been post-marketing reports of loss of consciousness, confusion, and mental impairment.
Withdrawal symptoms associated with pregabalin

(Pregablin SmPC (Pfizer) last updated 18.02.21)

- insomnia,
- headache,
- nausea,
- anxiety,
- diarrhoea,
- flu syndrome,
- nervousness,
- depression,
- pain
- convulsion
- hyperhidrosis
- dizziness
Emerging evidence of serious harms associated with non-medical use gabapentenoids (2013)

A case series of 10 patients admitted to an Emergency Department in Belfast over a one year period with pregabalin abuse.

- All were between 20-35 years old, with dosages ranging from 500-1400 mg.
- Nine were admitted for over 24 hours,
- 6 patients had seizures, and
- 2 patients were admitted to the Intensive Care Unit.

Bad medicine: gabapentin and pregabalin

Des Spence general practitioner, Glasgow

BMJ 2013;347:f6747
doi: 10.1136/bmj.f6747 (Published 8 November 2013)

business too, with combined sales worth £200m (€240m; $322m) a year. But a word of caution: pain and anxiety symptoms are subjective, with wide variation in reported prevalence. The longest neuropathic pain study lasted a mere 13 weeks, and highly psychoactive drugs are difficult to compare with placebo.

And there is increasing published evidence of concern about the abuse of pregabalin and gabapentin, and these drugs are now commonly being detected in toxicology in autopsies after drug overdoses. So what is the motivation to misuse these drugs? Users describe the effects as the “ideal psychotrophic drug,” “great euphoria,” “disassociation,” and “opiate buzz,” and are achieving these effects by taking large quantities as a single dose. Accordingly there is a growing black market, and these drugs are being bought through online pharmacies. The US recognises the problems associated with pregabalin, which has now become a scheduled drug under the Controlled Substance Act. Is the UK ignoring the misuse of pregabalin
Gabapentin and pregabalin: do the benefits outweigh the harms?
EE Morrison, EA Sandilands, DJ Webb

Misuse and Abuse of Pregabalin and Gabapentin: Cause for Concern?
Fabrizio Schifano

Gabapentinoids linked to new risks, including suicidal behaviour
Derek K Tracy consultant psychiatrist
Queen Mary's Hospital, London DA14 8LT, UK
ACMD review pregabalin and gabapentin (2016)

• “Pregabalin may have a higher abuse potential than gabapentin due to its rapid absorption and faster onset of action and higher potency. Pregabalin causes a ‘high’ or elevated mood in users; the side effects may include chest pain, wheezing, vision changes and less commonly, hallucinations.

• Gabapentin can produce feelings of relaxation, calmness and euphoria. Some users have reported that the ‘high’ from snorted gabapentin can be similar to taking a stimulant”

• 1 April 2019, pregabalin and gabapentin became Class C controlled substance (under the Misuse of Drugs Act 1971) and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3
Drug-related deaths in Scotland and NI where gabapentin and/or pregabalin were implicated in 2020

- **Scotland** (National Records of Scotland 2021)
  - 131 in 2015
  - 502 in 2020 (37% of all drug-related deaths).

- **N. Ireland** (N. Ireland Statistics and Research Agency 2021)
  - 15 in 2015
  - 77 in 2019
Deaths related to drug poisoning in England and Wales: 2020 registrations

- Numbers of deaths involving **benzodiazepines**
  - a rise of 19.3% from 399 (2019) to 476 deaths in 2020
- Numbers of deaths involving **pregabalin**
  - a rise of 41.0%; from 244 (2019) to 344 deaths in 2020
- Numbers of deaths involving **gabapentin**
  - a rise of 32.6%; from 89 (2019) to 118 deaths in 2020
- Number of deaths involving **zopiclone**
  - a rise of 4.3%; from 140 (2019) to 146 deaths in 2020
- Of the 796 deaths mentioning at least one of these substances, 93.5% (744 deaths) mentioned another drug, and 80.7% (642 deaths) mentioned an opiate.
Combining gabapentenoids with opioids increases overdose risk

- “For heroin users the combination of opioids with gabapentin or pregabalin potentially increases the risk of acute overdose death through either reversal of tolerance or an additive effect of the drugs to depress respiration”.

Advice for prescribers on the risk of the misuse of pregabalin and gabapentin

Pregabalin: reduce the daily dose at a maximum of 50-100mg/week.

Gabapentin: reduce the daily dose at a maximum rate of 300mg every four days.

No guidance on reducing from doses > 600MG DAILY
Reducing pregabalin and gabapentin following a period of stability

A suggested reduction regime for analgesic use would be:

- Gabapentin – reduce at maximum daily rate of 300mg every week
- Pregabalin - reduce at maximum daily rate of 50-100mg every week. In high risk patients, temporarily halt reduction, in preference to re-escalating the dose when required
- Rapid reduction to stop is justified if there is clear evidence of attempts to divert or obtain illicit supplies of gabapentin or pregabalin
- In practice, reduction regime may be adjusted depending on individual response and degree of associated risk.

Chronic Pain Prescribing Strategy – Effective Prescribing and Therapeutics (scot.nhs.uk)
Managing planned withdrawal from high dose non-prescribed pregabalin under care of addiction service

- Establish pregabalin dependence - history, examination, urine drug screens
- Drug diary + information leaflets + regular support
- Encourage reduction to lowest tolerated level as baseline, then reduce in 300mg dose to 600mg, then follow standard reduction regime 50-75 mg weekly but may need some flexibility
- Daily dispensing or monitoring of medication by significant other if prescribing pregabalin towards end of withdrawal
Managing planned withdrawal from pregabalin within an inpatient addiction unit

Admission to an inpatient addiction unit should be considered if:

- Continuing to use high doses pregabalin despite community based addiction treatment - urine drug screen to confirm use
- Co-morbidities - other substances, physical or mental health disorders
- Titrate dose against symptom – start 150- 300mg/day
- Unusual to need doses of ≥ 600mg/day in a hospital setting
- Aim to withdraw pregabalin within 3 weeks, depending on progress,
1.2.24 If the person cannot tolerate SSRIs or SNRIs, **consider offering pregabalin.**

As of 1 April 2019, pregabalin is a Class C controlled substance… Evaluate patients carefully for a history of drug abuse before prescribing and observe patients for development of signs of abuse and dependence (MHRA, Drug Safety Update April 2019). [2011, amended 2020]

1.2.25 **Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.** Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. [2011]

1.2.26 Do not offer an antipsychotic for the treatment of GAD in primary care. [2011, amended 2020]
MHRA has no plans to curb pregabalin prescribing by GPs

Exclusive The MHRA has confirmed that it does not currently plan to take regulatory action on pregabalin prescribing by GPs.

It comes after GPs in Northern Ireland were last month told they should no longer initiate prescriptions of pregabalin for neuropathic pain following a ‘significant increase’ in deaths related to the drug.

The drug was removed from the country’s formulary as the preferred option for the treatment of neuropathic pain but GPs will still be able to prescribe pregabalin where they deem it to be ‘clinically appropriate’.

Now the MHRA has confirmed to Pulse that it has no plans to limit prescribing of gabapentinoids, including pregabalin and gabapentin.

PREGABALIN WITHDRAWN FROM NI FORMULARY FOR NEUROPATHIC PAIN
June 2021
Drugs Map of Britain - Belfast Buds

Broadcast BB3 22 Jun 2017

https://youtu.be/8fc8sXWopBs
Final thought - should pregabalin be prescribed less or not at all and diazepam more often for GAD?

- “Alternatives to gabapentoids need to be recommended for clinicians managing opioid dependent patients with neuropathic pain or generalised anxiety, and greater attention given to restricting diversion of gabapentenoid prescriptions.”

Pregabalin - Guidance for people working with Pregabalin users.

Extern HSC Public Health Agency 2017

https://www.publichealth.hscni.net/sites/default/files/Pregabalin%20Guidance%20Booklet%20A4%20Final%20Web_0.pdf
Pregabalin Fact Sheet

**What is pregabalin?**
Pregabalin is a prescription drug used to manage a number of long-term conditions, including epilepsy, neuropathic pain, and generalized anxiety disorder. Similar to benzodiazepines, the analgesic (relieving) effects of pregabalin occur rapidly after administration.

**Pregabalin tablets**
Pregabalin comes in tablet form, in 25mg, 50mg, 75mg, 150mg, 200mg, and 300mg hard capsules. The colour of the capsule varies depending on the manufacturer. Some street names include: Lyrica, Gabrelin, Neurontin, Neurax. Neurafix.

**Pregabalin misuse**
Internationally, pregabalin misuse has been reported among individuals attending addiction services and recreational drug users. The relevant and sedative effects of pregabalin make it desirable for individuals to use unrelated to its prescribed recommendations. On online forums, pregabalin is reportedly taken in combination with other compounds in order to potentiate its effects, such as benzodiazepines, alcohol, heroin, poppy, methadone, marijuana, LSD, and amphetamine. Pregabalin was included on a list of new recreational substances and drugs (EPA) by the European Monitoring Centre for Drugs and Drug Addiction/European Union Early Warning System and has been monitored in this regard since 2009. Various reports support a growing illegal market for pregabalin, with it being easily accessed through illicit sources online, street, dealers, and counterfeitularities tablets being sold at over 300 percent above its normal cost. Pregabalin is sought after on the illicit drug market with tablets costing more than various other tablets available on the market.

**National Drug Treatment Centre Research**
A study in 2014 by the National Drug Treatment Centre (NDTC) Drug Analysis Laboratory confirmed that pregabalin abuse is taking place among the addiction services population. This study concludes that pregabalin has significant abuse potential and is an addictive drug to opioid-dependent drug users. It further suggests misuse of pregabalin as a serious emerging issue which should be monitored closely.

**Administration**
Pregabalin tablets are intended to be swallowed. When missed, pregabalin can be taken orally, intravenously (suitable, rapidly ingesting) or as a washout

**Short-term effects**
The effects of pregabalin can vary depending on the dose consumed. A range of experiences may be associated with pregabalin misuse, such as:
- Sedation
- Alcohol/GHB/benzodiazepine-like drunk effect
- Syncope
- A sense of relaxation and calm
- Hallucinations
- Lowered inhibitions
- Fatigue
- Blurred vision
- Constipation
- Tachycardia
- Trouble sleeping
- Psychosis
- Hypersomnia, confusion & memory impairment
- Tinnitus
- Tremors
- Peripheralsees (seeing in birds)
- Effects on vision
- Social effects (in a small number of people)

Pregabalin may be misused for recreational purposes to achieve specific mindsets or emotional connections and to cope with opioid withdrawal. Pregabalin has also been used to enhance the euphoric effects of other drugs, like opiate.

**Dependence**
Dependence has been reported among individuals using pregabalin outside of the prescribing recommendations. Tolerance and dependence can develop quickly to pregabalin.

**Withdrawal**
Suddenly stopping the use of pregabalin can be dangerous. Withdrawal from pregabalin should be slow and under medical supervision. Abrupt discontinuation of pregabalin may be associated with withdrawal symptoms such as:
- Insomnia
- Nausea
- Headaches
- Diaphoresis
- Dizziness
- Tremors
- Nervousness
- Severe coughing
- Depression
- Seizures
- Remission of pain or anxiety (if used to treat symptoms)

**Risks**
Pregabalin misuse can have a direct effect on the central nervous system (CNS) resulting in:
- Death
- Respiratory depression
- Sedation

Pregabalin has adverse effects on the CNS when used in combination with other CNS depressants. If more than one CNS depressant is used in combination with pregabalin (e.g., alcohol, benzodiazepines, small amounts of antihistamines, anti-emetics, anti-sedation), the use of pregabalin and alcohol can result in drowsiness, sedation, respiratory depression, and death. The risk of using pregabalin outside of its prescribed recommendations is greatly increased when used in combination with opiates (codine, heroin, methadon), benzodiazepines, tranquilizers, sleeping tablets, and alcohol (even small amounts). Try to use one drug at a time or two of less of each substance.

**Deaths**
Pregabalin and a similar drug, gabapentin, have been implicated in an increasing number of drug-related deaths across Europe in recent years.

In Ireland, pregabalin-related deaths increased by 88% from 2013 to 2014. In 2014, they further increased to 26% in 2014 to 26% in 2015.

In 2015, there were 50 drug-related deaths in Ireland and where pregabalin was mentioned on the death certificate. Gabapentin was listed on 49.

The University of Helsinki reviewed pregabalin and gabapentin involvement in opioid overdose deaths, noting that pregabalin misuse with high doses is increasingly common and can be fatal when combined with opiates. Further morbidity and mortality studies in Finland from 2010 to 2011 report that pregabalin was present in 31% cases.

**Treatment**
Literature in relation to the treatment of pregabalin dependence is limited. It is recommended that treatment is medically supervised and a slow withdrawal plan can be discussed with the prescribing doctor to meet the needs of each individual patient. A dose-reduction of the substance allows withdrawal symptoms to be managed as the dose of the drug is reducing.

**Pregabalin harm reduction information**
We recommend that all individuals should take pregabalin within its prescribing recommendations and under the supervision of a doctor. If necessary, they can consider to use pregabalin outside of its prescribing recommendations (misuse risk) then the following points are important to consider:

- Use one drug at a time and never mix drugs.
- Pregabalin and gabapentin are prescription drugs that may cause sedation. They are both misuse for the same effects as benzodiazepines or alcohol. Mixing benzodiazepines or alcohol with pregabalin and gabapentin can result in drowsiness, sedation, respiratory depression, and death. The risk of using pregabalin outside of its prescribed recommendations is greatly increased when used in combination with opiates (codeine, heroin, methadon), benzodiazepines, tranquilizers, sleeping tablets, and alcohol (even small amounts). Try to use one drug at a time or two of less of each substance.

“**To deliver excellent integrated services in partnership with our community**”
<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate half-life (hours)</th>
<th>Dose of oral benzodiazepine approximately equivalent to diazepam 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short- to intermediate-acting benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>1–3</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>4–15</td>
<td>15 mg</td>
</tr>
<tr>
<td>Temazepam</td>
<td>5–15</td>
<td>10 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>12–16</td>
<td>1 mg</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>6–25</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>20–30</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>16–48</td>
<td>5 mg</td>
</tr>
<tr>
<td>Clobazam</td>
<td>17–49</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>Long-acting benzodiazepines (includes effects of active metabolites)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>22–54</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20–80</td>
<td>5 mg</td>
</tr>
<tr>
<td><strong>Z-drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2.4</td>
<td>10 mg</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>5.2</td>
<td>7.5 mg</td>
</tr>
</tbody>
</table>

Brett J
Management of benzodiazepine misuse and dependence
Aust Prescriber
2015;38:152–5
Prescribing drugs of dependence in general practice
Part B - Benzodiazepines

Foreword

Benzodiazepines have a chequered clinical history and continue to produce polar opinions in the medical community. Benzodiazepines have been associated with both benefits and harms for patients, and a clear guide for accountable prescribing has been requested from multiple agencies.

Drug therapies will only ever have a partial role in managing complex bio-psychosocial issues that characterise mental health care. In the modern health environment, we have to explore and use non-drug therapies, and redefine the place of existing medications.

This guide represents a synthesis of the best available evidence for benzodiazepine use in the primary care setting. Consistent with all...
Material to support appropriate prescribing of hypnotics and anxiolytics across Wales

This educational pack aims to support the appropriate prescribing of hypnotics and anxiolytics across Wales by providing key health professionals with a practical approach for the initiation and review of hypnotic and anxiolytic prescribing. It includes examples of support material which can be used or adapted for this purpose.

It is anticipated that adoption of the ‘best practice’ examples presented within this pack will help to reduce the long-term prescribing of these drugs.

The pack was originally developed in 2011 by the Welsh Medicines Partnership (WMP) and has been previously updated (2016) to reflect changes in NICE guidance, the Misuse of Drugs Act and the Road Traffic Act. This update includes further amendments, in particular reflecting how the categorisation of insomnia has changed.

Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics Across Wales 818KB (PDF)

Published in July 2021 - replaces version previously published in December 2016

Pull-out sections (MS Word) - patient information is provided in both English and Welsh

- Appendix 1. Patient information leaflets
- Appendix 2. Assessment tools
- Appendix 3. Information for patients
- Appendix 4. Guides for healthcare professionals

Published July 2021
European Monitoring Centre for Drugs and Drug Addiction

- EMCDDA (2018) The misuse of benzodiazepines among high-risk opioid users in Europe
- EMCDDA (2021) New benzodiazepines in Europe – a review
- EMCDDA (2021) Non-medical use of medicines: health and social responses
SmPC Diazepam - Fertility, pregnancy and lactation

https://www.medicines.org.uk/emc/product/4523/smpc

(accessed online 24.10.21)

• “The safety of diazepam in human pregnancy has not been established…… should not be used in the first and third trimesters”.

• “There may be a small increase in the risk of congenital malformation, particularly oral cleft with the use of benzodiazepines in the first trimester but a causal relationship has not been established”.

• “If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.”
Guidance on all Benzodiazepines in Pregnancy
BNF (accessed online 24.10.21)

• Risk of neonatal withdrawal symptoms when used during pregnancy.
• Avoid regular use and use only if there is a clear indication such as seizure control.
• High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.
Safety of pregabalin in pregnancy

- Data is suggestive of a slightly increased overall risk of congenital malformations but there is uncertainty in the estimate of the increased risk;
- Very limited data exist on the risk of neurodevelopmental outcomes and these are suggestive of no increased risk; the data available from clinical studies do not allow any firm conclusion to be drawn and the risk remains uncertain; non-clinical data report on effects of pregabalin on fetal growth and development, but these effects were only seen at doses much higher than those used in humans.
- MHRA Antiepileptic drugs: review of safety of use during pregnancy Published 7 January 2021
SmPC Diazepam - Fertility, pregnancy and lactation

https://www.medicines.org.uk/emc/product/4523/smpc
(accessed online 24.10.21)

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- Avoid regular use and use only if there is a clear indication such as seizure control.
- High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.
Advice for pregnant women who take pregabalin

• “If you're trying to get pregnant or have become pregnant, you're routinely recommended to take at least 400mcg of a vitamin called folic acid every day.”

• “Pregnant women who take pregabalin are recommended to take a higher dose of folic acid. Your doctor might prescribe a high dose of folic acid (5mg a day) for you to take during the first 12 weeks of pregnancy.”

Pregabalin: medicine to treat epilepsy and anxiety - NHS (www.nhs.uk) (accessed 16.10.21)
Pregnancy

There are no adequate data from the use of pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Lyrica Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) (accessed 16.10.21)
bumps - best use of medicine in pregnancy (medicinesinpregnancy.org) (accessed 16.10.210)

**Are there any risks of taking pregabalin during pregnancy?**

There are no concerns that taking pregabalin in pregnancy causes miscarriage, birth defects, or low infant birth weight. One study has suggested that pregabalin use in later pregnancy might increase the chance of preterm birth.
Key conclusions on safety of pregabalin and gabapentin in pregnancy (MHRA 2021)

- “pregabalin may be associated with a slightly increased risk of major congenital malformations but further data are needed to reach a definitive conclusion;”
- the risks remain uncertain for gabapentin, oxcarbazepine, and zonisamide and the possibility of an increased risk can neither be confirmed nor ruled out;
- In relation to the risk of neurodevelopmental disorders the available non-clinical and clinical data are limited but that which is available supports that:
  - for gabapentin, oxcarbazepine, pregabalin, and zonisamide the data are either lacking or extremely limited and sometimes inconsistent, meaning that the risks remain uncertain and the possibility of an increased risk cannot be ruled out.

Source: MHRA Antiepileptic drugs: review of safety of use during pregnancy Published 7 January 2021
Recommendation for tapering benzodiazepines  Royal Australian College General Practice (2019)

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Recommended taper length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 to 8 weeks</td>
<td>Taper may not be required</td>
<td>Depending on clinical judgment and patient stability/preferece, consider implementing a taper, particularly if using a high-dose benzodiazepine or an agent with a short or intermediate half-life, such as alprazolam or triazolam</td>
</tr>
<tr>
<td>8 weeks to 6 months</td>
<td>Slowly over 2–3 weeks</td>
<td>Go slower during latter half of taper. Tapering will reduce, not eliminate, withdrawal symptoms. Patients should avoid alcohol and stimulants during benzodiazepine withdrawal</td>
</tr>
<tr>
<td>6 months to 1 year</td>
<td>Slowly over 4–8 weeks</td>
<td></td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>Slowly over 2–4 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Situation</th>
<th>Treatment Approach</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach to BZD dependence in general</td>
<td>Gradual withdrawal over a period of several weeks or months</td>
<td>High</td>
</tr>
<tr>
<td>Use of several BZDs or sedatives</td>
<td>Switch to use of only one BZD for detoxification (diazepam)</td>
<td>Good</td>
</tr>
<tr>
<td>Choice of BZD for detoxification</td>
<td>Switch to a long-acting BZD (diazepam)</td>
<td>Low</td>
</tr>
<tr>
<td>BZD withdrawal in a patient receiving opioid maintenance therapy</td>
<td>Adjustment of opioid dose to prevent opioid withdrawal; switch to a partial agonist (buprenorphine)</td>
<td>Good for adjustment of opioid dose; moderate for switch to partial agonist</td>
</tr>
<tr>
<td>Concomitant pharmacotherapy for BZD withdrawal</td>
<td>Carbamazepine, 200 mg twice a day</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Antidepressants, antihistaminergic drugs, melatonin; improved sleep hygiene, sleep restriction, relaxation techniques</td>
<td>Moderate</td>
</tr>
<tr>
<td>Other drugs for treatment of withdrawal symptoms</td>
<td>Pregabalin, gabapentin, beta-blockers; flumazenil</td>
<td>Low for pregabalin, gabapentin, and beta-blockers; experimental for flumazenil</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>Cognitive behavioral therapy and other approaches</td>
<td>Good</td>
</tr>
</tbody>
</table>

Soyka M, Treatment of Benzodiazepine Dependence  
• Broadcast May 26 2021

MAUDSLEY Webinar Series

BRAINCAST continues with Pospo and Professor Edward K. Silberman, on Benzodiazepines

https://youtu.be/ClSdj4CiZ8w
Guidance given by Professor Siberman during Maudsley webinar (24.05.21) (1)

• Withdrawal from benzodiazepines best managed by flexible withdrawal regime at a pace controlled by the patient
• Better to use fixed doses of benzodiazepines for chronic anxiety rather than prn doses
• Other psychotropic drugs may also cause withdrawal syndrome and cognitive impairment (e.g. Venlafaxine)
Guidance given by Professor Siberman during Maudsley webinar (24.05.21) (2)

- Avoid prescribing benzodiazepines to patients with:
  - Addictive disorders
  - Brain injury
  - Elderly
  - Individuals seeking sedative effects to deal with negative cognitions
Do Benzodiazepines Cause Alzheimer’s Disease?

• “little doubt that benzodiazepines, like other sedative hypnotics, may be associated with impaired cognition, usually mild, in a dose-dependent fashion.
• Usual recommendations are for the use of only short half-life benzodiazepines at low doses and, if clinically possible, for brief periods of time
• Pending further studies “we must assume that appropriate use of benzodiazepines will not lead to the development of Alzheimer’s disease.

Salzman C. Do Benzodiazepines Cause Alzheimer’s Disease?
Am J Psychiatry 177:6, June 2020 476-478
“Three types of clinical situation in which long-term prescribing of benzodiazepines may be considered defensible” (Ford 2014)

• In psychiatric illness, for the treatment of resistant, persistent severe anxiety or insomnia, panic disorder, generalised anxiety disorder, social phobia, dysphoric disorder, and anxiety due to medical illness

• 2. In benzodiazepine users, where there are withdrawal symptoms that are persistent, debilitating or intolerable and have tried everything with support and are unable to stop

• 3. As part of a harm reduction treatment, in those who have an inability to stay off alcohol or illicit benzodiazepines but in whom the harm reduces significantly when on a benzodiazepine prescription.

Ford C, Law F (2014) Substance Misuse Management Good Practice Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice