Austin HEALTH

Ask an Informationist

Choosing Wisely Australia

An initiative of NPS MedicineWise

WHAT IS THE EVIDENCE FOR THE USE OF

PREGABALIN

IN ACUTE NEUROPATHIC PAIN?

EVIDENCE OF AN ISSUE?

- Widely prescribed off-label for various pain syndromes – possibly as alternative to opioids?
- **1 in 7** Australians dispensed pregabalin – at high risk of misuse
- Victoria – **10x** increase in the number of pregabalin-related ambulance attendances during 2012-2017
- US – sales more than **doubled** since 2012
- UK – prescribing increased **350%** from 2007-2012

In Australia - only approved as second line treatment for neuropathic pain

Cairns et al. 2018; Crossin et al. 2019; Goodman & Brett 2019 & 2017; Murnion & Conigrave 2018; NPS 2018; Wettermark et al. 2014

EVIDENCE FOR USE IN SHINGLES?

Acute herpetic neuralgia = pain during first 30 days after onset of herpes zoster

- 2018 study – 45 patients: combination therapy (valaciclovir, methylprednisolone & pregabalin) had better efficacy than dual or single drugs
- 2016 study – 20 patients: pregabalin reduced pain compared with amitriptyline
- 2011 study – 45 patients: pregabalin reduced pain compared with placebo

scant evidence - further research required

Choudhary et al. 2018; Gabrani et al. 2016; Kanodia & Singhal 2011

EVIDENCE FOR USE IN SCIATICA?

"... appears to be ineffective in patients with sciatica"

- pregabalin did not significantly reduce intensity of leg pain nor improve other outcomes
- incidence of adverse events substantially higher than placebo
- recent trials do not exclude possible benefit in chronic sciatica

Attal & Barrot 2017; Enke et al. 2018; Mathieson et al. 2017

RISKS & CONCERNS?

"Clinicians should be cautious about prescribing pregabalin ... consider whether its benefits outweigh potential harms"

- addiction potential – particularly with patient history of opioid abuse
- comparative research shows a high prevalence of adverse effects in relation to the number of users
- may improve postoperative analgesia at the expense of increased sedation and visual disturbances
- greater transparency required with independent, publicly funded trials encouraged

Baftiu et al. 2019; Bonnet & Scherbaum 2017; Evoy et al. 2017; Onakpoya et al. 2019

Pregabalin – evidence for use in acute neuropathic pain

Pregabalin is indicated for the treatment of neuropathic pain and epilepsy.
In Australia it is 'only PBS listed for people with refractory neuropathic pain not controlled by other drugs'.

Sources: Australian Medicines Handbook 2019; NPS MedicineWise 2018

> *"… we suspect that clinicians who are desperate for alternatives to opioids have lowered their threshold for prescribing gabapentinoids to patients with various types of acute, subacute, and chronic noncancer pain."*
>
> *Source: Goodman & Brett New England Journal of Medicine 2017; 377: 411-414*

Evidence of an issue?

A clinical overview of off-label use of gabapentinoid drugs

- "The gabapentinoid drugs gabapentin and pregabalin were originally developed as antiseizure drugs but now are prescribed mainly for treatment of pain."
- "This report summarizes the limited published evidence to support off-label gabapentinoid uses, describes clinical cases in which off-label use is problematic, and notes how review articles and guidelines tend to overstate gabapentinoid effectiveness."
- "Clinicians who prescribe gabapentinoids off-label for pain should be aware of the limited evidence and should acknowledge to patients that potential benefits are uncertain for most off-label uses."

Source: Goodman & Brett. JAMA Internal Medicine 2019; online first 25 March

Pregabalin misuse-related ambulance attendances in Victoria, 2012-2017: characteristics of patients and attendances

- "There were 1201 pregabalin misuse-related attendances during the study period; the rate increased from 0.28 cases per 100 000 population in the first half of 2012 to 3.32 cases per 100 000 in the second half of 2017."
- "The attendance rate was strongly correlated with prescription rates in Australia."
- "Pregabalin was frequently misused with other sedatives (812 attendances, 68%), particularly benzodiazepines (440, 37%); 472 attendances (39%) were associated with suicide attempts."
- "Caution is required when prescribing pregabalin for people taking other sedatives. Limiting the dispensing of this drug may reduce the risks associated with its misuse."

Source: Crossin et al. MJA 2019; 210(2): 75-79

Critical review report: Pregabalin

- "In the UK, prescriptions for pregabalin have increased more than 11-fold in the last decade, from 476,102 in 2006 to 5,547,560 in 2016."
- "According to Pharma Marketing (2018), worldwide sales of pregabalin (Lyrica) in 2017 reached 10th position in terms of gross sales (about 5.1 billion USD), with an annual growth rate of about 2.8%."

Source: World Health Organization critical review report: Pregabalin Expert Committee on Drug Dependence 41st meeting 2018

Pregabalin misuse: the next wave of prescription medication problems

- "The fundamental problem that much current pregabalin prescribing is probably inappropriate has also been recognised."
- "The sharp rise in the numbers of deaths attributed to prescription opioids has led to prescribers appropriately reconsidering prescribing them for people with persistent pain."
- "Pregabalin may be prescribed more frequently for chronic non-malignant pain in the perception that it is safer than opioid medications."

Source: Murnion & Conigrave. MJA 2018: online first 13 December

Pregabalin and gabapentin: what impact will reclassification have on doctors and patients

- "From 1 April 2019 pregabalin and gabapentin will be reclassified as class C controlled substances in the UK."
- "The reclassification will make it illegal to supply pregabalin and gabapentin through repeat dispensing. Pharmacists will need to dispense the drugs within 28 days of a prescription being written, and doctors will have to hand sign prescriptions."

Source: Torjesen. BMJ 2019; 364: I1107

Rising pregabalin use and misuse in Australia: trends in utilisation and intentional poisonings

- "There has been a dramatic increase in pregabalin use, poisonings and deaths in Australia since it became subsidized publicly in 2013."
- "One in seven Australians dispensed pregabalin appears to be at high risk of misuse."
- "Pregabalin was the 10th most prescribed medicine in the United States in 2016, and sales have more than doubled since 2012."
- "Pregabalin prescribing in the United Kingdom increased by 350% from 2007 to 2012."
- "In Ontario, Canada, pregabalin usage increased 22-fold in 2013–14."
- "A Swedish study revealed that 8.5% of patients receiving pregabalin were dispensed more than the maximum dose (600 mg/day)."
- Pregabalin was ranked sixth in the top subsidised drugs in Australia in 2016–17.

Source: Cairns et al. Addiction 2018; online first: 11 August

Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment

- The issue of potential off-label prescribing or poor registration of diagnoses should also be noted as a high proportion had been prescribed the drug without a record of any of the approved indications.

Source: Wettermark et al. International Journal of Clinical Practice 2014; 68(1): 104-110

What is the evidence for the use of Pregabalin in shingles?

Acute herpetic neuralgia

Safety and efficacy of different systemic treatment modalities for acute pain of herpes zoster: a pilot study

- "The aim of this study was to compare the efficacy and side-effects of different systemic treatment modalities for acute herpes zoster neuralgia."
- Sample size of this study was limited (n=45).
- "Combination therapy with valacyclovir [Valaciclovir], methylprednisolone, and pregabalin has better efficacy compared to valacyclovir [Valaciclovir] and pregabalin and valacyclovir [Valaciclovir] alone in the management of acute herpes zoster neuralgia. No significant side-effects were observed."
- "Further studies with large sample size are required to further validate the findings of the present study."

Source: Choudhary et al. Indian Dermatology Online Journal 2018; 9(2): 101-104

Effectiveness of pregabalin compared with amytriptilin [amitriptyline] in acute herpetic neuralgia

- Small study of 20 patients to determine the effectiveness of pregabalin compared with amitriptyline in acute herpetic neuralgia.
- Pregabalin was found to significantly reduce pain in acute herpetic neuralgia patients.

Source: Gabrani et al. Neurology 2016; 86(16 Supplement): P2.255

A study on efficacy of Pregabalin in acute herpetic neuralgia

- This study examined the efficacy and safety of pregabalin in reducing the pain of acute herpetic neuralgia; the study was a placebo-controlled 4 week trial which included 45 subjects.
- "Subjects receiving pregabalin had a statistically significant reduction ($p<0.0001$) in visual analogue scale(VAS) score as compared to placebo".
- "Side effects most commonly noted were somnolence and dizziness."

Source: Kanodia & Singhal. Annals of Neurosciences 2011; 18(4): 148-150

Research indicating use of pregabalin in this cohort:

Acute herpes zoster and post herpetic neuralgia in primary care: a study of diagnosis, treatment and cost

- "This was a cross-sectional observational study by means of a quantitative survey of 1,000 general practitioners registered in Ireland exploring the frequency of diagnosis, methods of treatment and cost of AHZ [acute herpes zoster] and PHN [post herpetic neuralgia] in primary care."
- "Mild opioids (32%) were the most common analgesic agents used for first line AHZ pain, and pregabalin (37%) the most commonly prescribed analgesic agent for second line AHZ pain."

Source: Crosbie et al. European Journal of Clinical Microbiology and Infectious Diseases 2018; 37(4): 627-631

What is the evidence for the use of Pregabalin in sciatica?

2018 Update on medical overuse

- "Pregabalin appears to be ineffective in patients with sciatica."
- "A recent meta-analysis of 9 randomized trials evaluated the effectiveness of anticonvulsants in patients with low back pain and found minimal to no pain relief with these medications, yet the significant adverse effects included dizziness, fatigue, and difficulties with mentation."
- "These results remind physicians to limit prescribing of gabapentinoids to conditions and patients for whom direct evidence supports benefits that will outweigh the well-described potential harms."

Source: Morgan et al. JAMA Internal Medicine 2019; 179(2): 240-246

Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis

- "There is moderate- to high-quality evidence that anticonvulsants are ineffective for treatment of low back pain or lumbar radicular pain."
- "There is high-quality evidence that gabapentinoids have a higher risk for adverse events."

Source: Enke et al. 2018; CMAJ: Canadian Medical Association Journal 190(26): E786-E793

Trial of pregabalin for acute and chronic sciatica

- "Treatment with pregabalin did not significantly reduce the intensity of leg pain associated with sciatica and did not significantly improve other outcomes, as compared with placebo, over the course of 8 weeks."
- "The incidence of adverse events was significantly higher in the pregabalin group than in the placebo group."

Source: Mathieson et al. The New England Journal of Medicine 2017; 376(12): 1111-112

Is pregabalin ineffective in acute or chronic sciatica?

- "In contrast to large-scale trials of pregabalin for neuropathic pain that were conducted between 2003 and 2010 and that showed positive results, the results of randomized, controlled trials that were conducted during the past 5 years have tended to show either negative results or minimal effects."
- A recent meta-analysis included "trials with negative outcomes that were reported on ClinicalTrials.gov but were unpublished", showed need to treat 7.7 patients for 1 patient to achieve 50% pain relief.

Source: Attal & Barrot. The New England Journal of Medicine 2017; 376: 1169-1170

Pregabalin and gabapentin for the treatment of sciatica

- The efficacy, side effects profile and cost of pregabalin (PGB) and gabapentin (GBP) in neuropathic pain states were reviewed with special reference to sciatica.
- The amount and quality of evidence was low, and only indirect comparisons were available. Importantly, no direct "head-to-head" study existed.
- "Despite weak data, and having cited minor titration, but definite cost advantages, UK National Institute for Health and Clinical Excellence favoured PGB over GBP."

Source: Robertson et al. Journal of Clinical Neuroscience 2016; 26: 1-7

Evidence of risks & concerns?

Safety aspects of antiepileptic drugs—a population-based study of adverse effects relative to changes in utilisation

- The purpose of the present study was to characterise adverse effects reports of antiepileptic drugs (AEDs) in Norway relative to changes in utilisation in various indications from population-based data.
- "This study demonstrates that most adverse effects reported concerned AEDs increasingly used in non-epilepsy indications: neuropathic pain (pregabalin, gabapentin, carbamazepine) and psychiatry (lamotrigine, valproate, carbamazepine)."
- "Pregabalin had the highest prevalence of adverse effects reported in relation to number of users."
- "This elucidates an important part of pharmacovigilance for improved safety and considerations in clinical practice."

Source: Baftiu et al. European Journal of Clinical Pharmacology 2019; online first 18 April

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomised clinical trials

- "Clinicians should be cautious about prescribing pregabalin and should consider whether its benefits outweigh potential harms in individual patients."
- "The evidence from RCTs in journal publications suggests that pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of adverse events and discontinuation due to adverse events."
- "The quality of the evidence from journal publications is overall low, and the duration of trials is short."
- "Greater transparency in the reporting of outcomes is advocated; independent and publicly funded trials assessing the effects of pregabalin in neuropathic pain should be encouraged."

Source: Onakpoya et al. BMJ Open 2019; 9(1): e023600

How addictive are gabapentin and pregabalin? A systematic review

- "In the last ten years, gabapentin and pregabalin have been becoming dispensed broadly and sold on black markets, thereby, exposing millions to potential side-effects.
- Meanwhile, several pharmacovigilance-databases have warned for potential abuse liabilities and overdose fatalities in association with both gabapentinoids."
- Reviewers concluded that in patients with a history of substance use disorders "gabapentinoids should be avoided or if indispensable, administered with caution by using a strict therapeutic and prescription monitoring."

Source: Bonnet & Scherbaum. European Neuropsychopharmacology 2017; 27(12): 1185-1215

Abuse and misuse of pregabalin and gabapentin

- This review assessed the "extent of gabapentinoid abuse, characteristics of typical abusers, patterns of abuse, and potential harms in order to bring this trend to providers' attention."
- "Evidence suggests gabapentinoids possess potential for abuse, particularly in individuals with a history of opioid abuse, and reports of such abuse are increasingly being documented. Prescribers should be aware of high-risk populations and monitor for signs of abuse."

Source: Evoy et al. Drugs 2017; 77(4): 403-426

Further reading

Systematic review evidence for acute and chronic pain

Pregabalin for acute and chronic pain in adults

- Reviewers assessed "analgesic efficacy and associated adverse events of pregabalin in acute and chronic pain."
- Findings showed "pregabalin has proven efficacy in neuropathic pain conditions and fibromyalgia."
- "A minority of patients will have substantial benefit with pregabalin, and more will have moderate benefit. Many will have no or trivial benefit, or will discontinue because of adverse events."
- "Individualisation of treatment is needed to maximise pain relief and minimise adverse events."
- "There is no evidence to support the use of pregabalin in acute pain scenarios."

Source: Moore et al. Cochrane Database of Systematic Reviews 2009; (3): CD007076

In 2019 this review was updated as follows:

Pregabalin for neuropathic pain in adults

- Reviewers assessed the analgesic efficacy and adverse effects of pregabalin for chronic neuropathic pain in adults.
- The reviewers note "**the information about acute pain is unchanged and probably out of date**, mainly because the clinical question is now different."
- A separate updated review of pregabalin for fibromyalgia has been published (see Derry et al. Pregabalin for pain in fibromyalgia in adults. Cochrane Database of Systematic Reviews 2016; (9): CD011790)
- "Pregabalin at daily oral doses of 300 to 600 mg can provide good levels of pain relief for some people with postherpetic neuralgia and painful diabetic neuropathy. Evidence for other types of neuropathic pain is very limited."
- "More than half of those treated with pregabalin will not have achieved worthwhile pain relief" (e.g. greater than 50% pain intensity reduction).
- "Around 6 or 7 out of 10 will experience at least one adverse event with pregabalin (somnolence and dizziness are common), compared with 5 or 6 out of 10 with placebo.
- Serious adverse events are rare and are of similar proportions with pregabalin and placebo.
- The level of efficacy found for pregabalin is consistent with efficacy estimates for other drug therapies for chronic neuropathic conditions."

Source: Derry et al. Cochrane Database of Systematic Reviews 2019; (1): CD007076