Pregabalin

Pregabalin is now fully funded without restrictions both in hospitals (Hospital Medicines List) and in the community (PHARMAC Schedule). As the use of newly available medicines, particularly new medicines within a class, presents some challenges to clinicians the aim of the below is to familiarise clinicians with pregabalin's pharmacology and place in therapy and to compare it to gabapentin which is also now fully funded without restriction.

Pregabalin vs gabapentin[6]

	pregabalin	**gabapentin**
structure	synthetic analogue of gamma-aminobutyric acid (GABA)	A different synthetic analogue of gamma-aminobutyric acid (GABA)
pharmacodynamics	Binds to calcium channels and reduces release of excitatory neurotransmitters	Same as pregabalin
pharmacokinetics		
Time to peak concentrations	1 hour (2 to 3 hours with food)	3 to 4 hours
Oral bioavailability	Linear with dose	Saturable - 60% available at 900 mg and 33% at 3600 mg per day
Excretion	Renal unchanged (99%)	Renal unchanged (99%)
Doses for neuropathic pain	25 to 600 mg per day in up to 2 divided doses: initially 75 mg PO BD (some centres start on 25 mg BD) increasing after 3 to 7 days to 150 mg PO BD and again after 7 days to 300 mg PO BD if necessary (normal renal function). Use **lower increments in those on opioids.** Adjust dose in renal dysfunction and in older patients.	150 to 3600 mg per day in up to 3 divided doses, starting low and increasing slowly. Adjust dose in renal dysfunction and in older patients.

Indications, Efficacy and Safety

- Pregabalin is used to treat neuropathic pain, focal seizures and generalised anxiety (unlicensed)
- A Cochrane[1] review assessed the efficacy and adverse effects of pregabalin in neuropathic pain and fibromyalgia. The authors concluded that a minority of patients will get substantial benefit from pregabalin, more will get moderate benefit and many will get no to minimal benefit or will stop taking it due to adverse effects.
- A recent systematic review and meta-analysis into the prevention of chronic postsurgical pain found in the 3 trials evaluated a decrease in the incidence of chronic pain postoperatively after a short course of pregabalin[2]
- In the book 'Acute Pain Management - Scientific Evidence 4th Edition 2015[3] various sources sited concluded that:
    - perioperative pregabalin or gabapentin improve analgesia, reduce postoperative opioid consumption, and reduce opioid related adverse effects (nausea, vomiting, urinary retention, pruritis), but increase the incidence of sedation and visual disturbance.
    - the perioperative use of pregabalin or gabapentin to reduce chronic post-surgical pain across a diverse range of procedures is of uncertain benefit. Some individual studies show promising results, however meta-analyses are less conclusive.
    - Pregabalin and gabapentin are effective in the treatment of neuropathic pain, diabetic polyneuropathy, fibromyalgia, postherpetic neuralgia.
- Adverse effects of pregabalin (dose related):
    - A systematic review and meta-analysis of randomised controlled trials found 20 adverse effects were significantly associated with pregabalin including balance disorder with a relative risk of 8 (highest), euphoria 6 and incoordination 5.[4] Other adverse effects include dizziness, somnolence, dry mouth, oedema and blurred vision (also seen with gabapentin). **Additive CNS adverse effects** are seen with opioids e.g. respiratory depression – monitor closely.
    - **Gabapentin and pregabalin should not be used together.**
- Abuse potential
    - *Pregabalin and gabapentin can be associated with withdrawal symptoms and have the potential to be abused.*[5]
    - In the UK both gabapentin and pregabalin are to be reclassified as Controlled Drugs following an increase in abuse, misuse and deaths linked to their use due to their ease of access. In England and Wales the number of deaths linked to pregabalin rose from 4 in 2012 to 111 in 2016. The number linked to gabapentin rose from 8 to 59 in the same period.[7]

Conclusion

- Pregabalin appears to be an effective analgesic in some patients particularly those with neuropathic pain
- Dosing needs to be adjusted for renal function and in older patients
- Adverse effects are mainly CNS and dose related. Abuse potential exists and should be taken into account especially if prescribing on discharge

Refs
1. Moore et al Pregabalin for acute and chronic pain in adults (review) Cochrane database of systematic reviews 2009 issue 2. Clarke et al The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis Anaesthesi and Analgesia August 2012 115 no.2 3. 'Acute Pain Management - Scientific Evidence 4th Edition 2015 Australian and New Zealand College of Anaesthetists 2015 ISBN Print: 978-0-9873236-7-5 Online: 978-0-9873236-6-8 4. Zaccara et al The adverse event profile of pregabalin: a systematic review and meta-analysis of randomised controlled trials Epilepsia 2011 52 4 826-836 5. Schjerning et al Abuse potential of pregabalin – a systematic review CNS Drugs 2016 DOI10.1007/s40263-015-0303-6 6.Bockbrader H et al A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin 2010 Clin Pharmacokinetics 49 10 661-66 7. Iacobucci G UK government to reclassify pregabalin and gabapentin after rise in deaths. BMJ 2017;358:j4441 doi: 10.1136/bmj.j4441