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Therapeutic Brief

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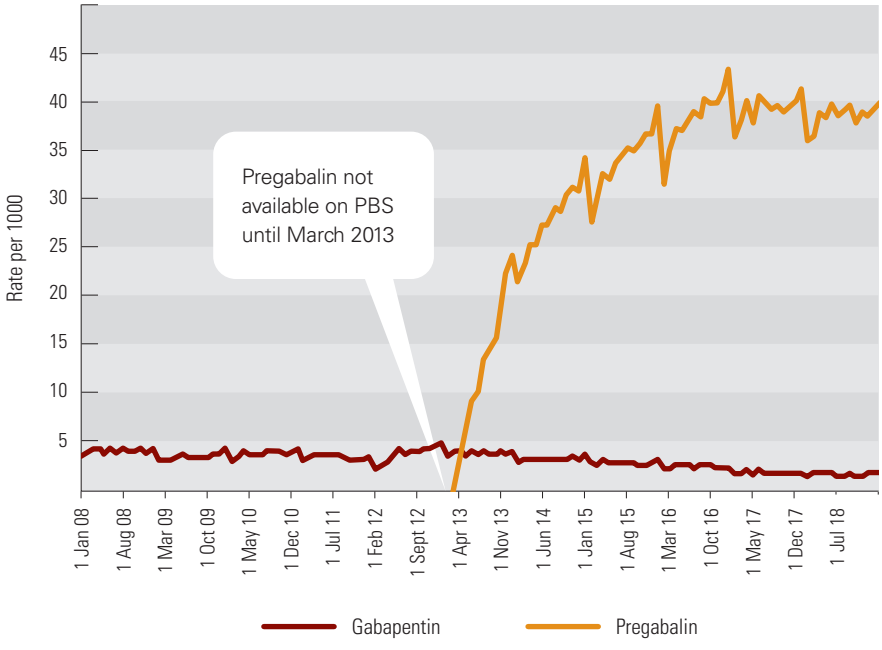
Reviewing your patients on gabapentinoids

Managing pain can be difficult particularly with the limitations of current treatment options. There are concerns about the over-use of opioids in people with chronic pain, and the safety of non-steroidal anti-inflammatory drugs (NSAIDs) in many patients including the elderly, and people with impaired renal function or cardiovascular disease. These factors may have contributed to increasing use of the gabapentinoids, pregabalin and gabapentin (see Figure 1).[1-6]

The use of gabapentinoids can present particular challenges. In the elderly, sedation and dizziness can occur in up to 40% and 50% of patients, respectively, increasing the risk of falls and cognitive impairment.[7] Intentional and unintentional misuse of gabapentinoids has increased worldwide.[1,2]

This therapeutic brief aims to assist in the review of the care of your DVA patients on gabapentinoids.

Figure 1. Rate of DVA patients dispensed gabapentin and pregabalin per 1000.[3]



INSIDE

Key points

- Use a multi-modal management approach to help your patients understand the three key components of pain: emotion, cognition and sensation
- Before re-prescribing a gabapentinoid, review your patient's clinical situation and any benefit from the gabapentinoid; modify the dose or cease where appropriate
- If your patient could benefit from further support, consider referral to a psychologist so they can learn techniques to better understand their pain

Current understanding of pain

Pain, whether acute or chronic, is a complex interplay of emotion, cognition and sensation, and is not a simple reflection of tissue or nerve damage.[5,8-10] Factors that can influence the perception of pain include cultural and social norms, expectations, past experiences, beliefs, stress and fatigue. The pain experience can be amplified or dampened by moderating any of these factors.[11-13] The brain achieves this pain response via the dopamine (reward) system and the limbic (emotions, motivations, learning and memory) system. The brain interprets signals from multiple sources to determine the perceived level of threat or danger.[10]

Pain is generally considered chronic (or persistent) if it lasts longer than three months. This includes neuropathic pain, which is pain caused by a lesion or disease of the somatosensory system. Neuropathic pain has a wide variety of causes, for example post herpetic neuralgia and diabetic peripheral neuropathy.[5,6,14] Pain can also present as a combination of both nociceptive and neuropathic elements.

A holistic model that recognises the physical, psychological, social and environmental factors contributing to the experience of pain for an individual is now widely accepted as the best care.[5,8,11-18]

The review process

The aim of the review process is to gradually shift the focus from the prescription of medicines to helping your patient gain a better understanding of pain and self-management strategies. The review process may need a series of small interventions over a number of consultations.[15]

Step 1: Explore your patient's understanding of pain

Patients who feel heard and understand their pain feel more in control and experience less pain.[8,11,16-19]

Explore your patient's beliefs about the causes and consequences of their pain. Gaining an understanding of the cognitive (thoughts about pain), emotive (the meaning given to pain, influenced by mood, memory and learning) and sensory factors contributing to their pain, can help your patient recognise and reframe unhelpful thoughts, emotions and behaviours.[9-13,19,20] Help your patients gain realistic expectations about their pain and the limited role of medicines in managing pain.

Step 2: Plan strategies to support self-management

Interventions that support and empower patients to self-manage are recommended when treating chronic pain.[5,16,21] The choice of interventions will depend on the contribution that sensory, emotional and cognitive factors make to the pain experience.

Is pain education required?

Explaining the science of pain helps to reconceptualise pain as less threatening and improves movement and sleep, and reduces fear-avoidance.[12,13,16,21]

Education that enhances a person's understanding about their pain can help patients to recognise and modify thinking and beliefs. Using metaphors and stories as part of pain education improves understanding and reduces catastrophising behaviours related to pain.[8,13,16,22]

Education about pain is effective face-to-face or with written and online material, and can be successfully provided by all health professionals (see Box 2).[9,13,16]

Would tailored psychological therapies be beneficial?

Psychological therapies for pain management aim to improve the patient's functioning and quality of life and include cognitive behavioural therapy (CBT) and acceptance and commitment therapy.[9,11,17,21]

Negative thought and beliefs, or catastrophising thoughts, can lead to maladaptive coping and increased pain.[9,15] When this is related to lack of improvement or a barrier to other therapies, consider referral to a psychologist for CBT.

CBT can help modify thoughts, feelings and behaviours associated with chronic pain. It provides techniques and coping strategies to increase your patient's control over pain, and how they interpret and manage it. CBT also helps reduce distress and catastrophising, provides strategies to divert focus from pain and increase physical activity, and includes relaxation training.[8-12,16]

If your patient has a strong emotional response to pain consider referring them to a psychologist for CBT or acceptance and commitment therapy (see Box 2).[5,8,9,21]

Will increased physical activity help?

Safe, regular movement helps reduce pain, reverses the effects of deconditioning, improves strength, and decreases self-perceptions of disability.[15,16]

Physical treatments aim to promote self-management. Develop a movement plan that includes activities that are meaningful, enjoyable and measurable.[16] Encourage your patient to use a 'paced' approach to exercise.[5,8,9,16]

Consider referral to a physiotherapist, exercise physiologist or occupational therapist to assist in the development of an achievable plan (see Box 2).

DVA pays for Gold and some White Card holders to receive services from psychologists, physiotherapists, exercise physiologists and pain management specialists. For queries on eligibility for white card holders, phone the DVA general enquiries number, 1800 555 254.

Step 3: Review the gabapentinoids

Gabapentinoids need to be used with caution in all people, but particularly in those at higher risk of harm due to comorbidities or concurrent use of psychoactive medicines, for example benzodiazepines or opioids, or use of other substances such as alcohol or cannabis (see Box 1).[1,2,6,23]

Review ongoing need

Use available tools to accurately diagnose or review neuropathic pain and avoid gabapentinoids when pain does not satisfy neuropathic diagnostic criteria.[16,24]

See the NPS MedicineWise demonstration video of physical examination sensory tests, available at: www.nps.org.au/professionals/neuropathic-pain#resources and the classification of neuropathic pain tool, DN4, at:

www.aci.health.nsw.gov.au/chronic-pain/health-professionals/assessment A total score >4 is suggestive of neuropathic pain.

If your patient's pain is not neuropathic, carefully review and consider the potential benefits and harms of prescribing gabapentinoids. See Table 1 for information on gabapentinoid dosing.

Gabapentin and pregabalin have been shown to modestly decrease pain associated with post herpetic neuralgia and diabetic peripheral neuropathy.[24-26] Pregabalin, but not gabapentin, has modest benefit for neuropathic pain associated with spinal cord injury and fibromyalgia.[25] A dose-response effect has been shown for pregabalin but not for gabapentin.[25,26] **Only about one in eight patients treated with a gabapentinoid for neuropathic pain will benefit.[24,25]** Neither gabapentin nor pregabalin has been shown to be effective in other pain conditions, such as sciatica or low back pain, which resolves within six weeks without treatment in 40% to 70% of people.[27-29] Failure to respond to gabapentin does not predict failure to respond to pregabalin and vice versa. The tolerability and efficacy of different gabapentinoids may vary in individual patients.[4]

Review the dose

Aim for the lowest effective dose to achieve ongoing demonstration of functional benefit and review the response after an eight week treatment trial; **periodically attempt dose reduction to avoid harm (see Table 1).[8,24,30]**

Review patients on high doses of gabapentinoids i.e. >600 mg daily for pregabalin and >3,600 mg daily for gabapentin. Absorption of gabapentin is saturable; plasma concentrations of gabapentin do not increase proportionally with increasing dose. Consider reducing the dose or tapering with the aim of ceasing, depending on circumstances. Evidence of dose escalation or patients requesting high doses may be an indication of misuse; if suspected, manage accordingly.[2,31]

Up to half of all patients prescribed gabapentinoids are taking very low doses, not consistent with guidelines for neuropathic pain.[32] Potentially subtherapeutic daily doses for neuropathic pain are less than 75 mg for pregabalin and less than 300 mg for gabapentin. Check for lack of functional benefit and consider tapering and stopping the gabapentinoid if your patient is unable to tolerate a therapeutic dose. Review the reason for prescribing.

Gabapentinoids can also cause sleep disturbance, similar to alcohol use.[2] Consider non-pharmacological options for sleep to help patients who are ceasing gabapentinoids. For more information, see the Veterans' MATES topic: *Helping veterans learn to sleep well at*: www.veteransmates.net.au/topic-55-therapeutic-brief

Be mindful of the patient's renal function, as dose reduction is required in renal impairment.[14] For more details see the Veterans' MATES topic *Medicines and your kidneys* at: www.veteransmates.net.au/topic-56

Always titrate the dose cautiously to minimise adverse effects and improve tolerability.[24,27]

Review the duration

Maximise the use of non-pharmacological strategies and periodically try dose reduction of medicines to assess ongoing need and to reduce harm.[8,15,24]

Allow sufficient time for the onset of action. Review medicine use after three to six months. The trials looking at duration of use of gabapentinoids are not longer than three months.[25,30]

Avoid abruptly stopping gabapentinoids, as resulting withdrawal symptoms including insomnia, nausea, headache, anxiety, sweating and diarrhoea can last up to 12-24 weeks.[6,14,24]

Explain to your patients that medicines for pain require ongoing review and do not need to be maintained indefinitely, particularly if they are no longer effective in helping achieve individual goals such as improved function and quality of life.[15]

Review for adverse effects

Up to 50% of patients taking gabapentinoids experience adverse effects which are dose-related, occurring more frequently at initiation or after dose increase.[6] Adverse effects include sleepiness and dizziness, ataxia, confusion, memory impairment, dry mouth, euphoria, suicidal ideation, impaired balance, weight gain, and oedema.[14] Caution should be taken when using gabapentinoids in people with heart failure.

There is a risk of misuse of gabapentinoids which is likely to be related to their dopaminergic effects and occurs more frequently in people with mental health conditions such as depression, anxiety and post-traumatic stress disorder or a history of substance misuse. Supratherapeutic doses may cause sedation, dissociation, uninhibited behaviour and hallucinations.[1,2,4,24] Review for adverse effects and potential misuse.

Step 4: Review other medicines

Gabapentinoids and other medicines used in the management of neuropathic pain should be used only as adjuncts to non-pharmacological strategies as part of a multi-modal plan, with the aim of improving quality of life and function.[8,14-16]

Initially, a trial of paracetamol or an NSAID (if safe for the patient) is recommended as the pain may have mixed nociceptor and neuropathic elements.[8,21,24]

If more than one medicine for neuropathic pain is being used, review for benefit or adverse effects and consider ceasing medicines. Consider amitriptyline as the preferred first line agent for neuropathic pain.[8,24]

Review the need for any other medicines including analgesics and sedatives every six months and before each re-prescription to ensure the goals of therapy are being met.

Box 1. Avoid combining gabapentinoids and opioids or other CNS depressants

Although gabapentinoids are sometimes used as an adjunct to opioids for neuropathic pain, evidence for the benefit of this combination is limited.[21] Caution is needed when using combinations as there is greater risk of toxicity and death.[2,21,23] Additive toxicity can also occur when gabapentinoids are combined with other centrally acting medicines such as benzodiazepines and alcohol. Pregabalin-associated deaths are commonly linked with opioid, benzodiazepine or illicit drug use.[1,2,23] Combining gabapentinoids and opioids is associated with a 49% increased risk of dying of opioid-related causes such as respiratory failure.[23]

Consider referring your patients for a Home Medicines Review to review medicines for pain.

Table 1 Gabapentinoid dosing information

	Gabapentin	Pregabalin
Usual dose	Initially 100–300 mg at night, then increase gradually every 3–7 days to 0.9–2.4 g daily in 3 doses, maximum 3.6 g daily.[14,27] Allow sufficient time for the effectiveness of the dose to be determined. In older patients use lower initial doses, e.g. 100 mg daily.	Initially 25–75 mg at night for 3–7 days, then increase dose gradually at 7–14 day intervals as needed,[27,30,31,33] e.g. 150 mg daily in 1 or 2 doses, to 150 mg twice daily; maximum 300 mg twice daily. Allow sufficient time for the effectiveness of the dose to be determined. For older or frail patients, a lower initial dose (e.g. 25 mg at night) or a slower dose titration may improve tolerability. Giving a larger portion of the dose in the evening may reduce daytime sedation.
Dose in renal impairment	Adjust maintenance dose according to creatinine clearance (CrCl):[14] **50–79 mL/minute:** 0.6–1.8 g daily in 3 doses **30–49 mL/minute:** 300–900 mg daily in 2 or 3 doses **15–29 mL/minute:** 300 mg once every 2 days up to 600 mg daily in 2 or 3 doses **<15 mL/minute:** 300 mg once every 2 days up to 300 mg once daily	Adjust dose according to CrCl:[14] **30–60 mL/minute:** initially 75 mg daily; maximum 300 mg daily in 1 or 2 doses **15–30 mL/minute:** initially 25–50 mg daily; maximum 150 mg daily in 1 or 2 doses **<15 mL/minute:** initially 25 mg daily; maximum 75 mg as a single dose
Stopping treatment	Reduce dose gradually over at least a week, e.g. by 300 mg daily every 4 days.[6,14,31]	Reduce dose gradually by 50–150 mg daily over at least a week, e.g. if starting from 600 mg, reduce to 450 mg for 2 days, 300 mg for 2 days, 150 mg for 2 days, then cease.[6,14,31]
	Reassure the patient and explain the reasons for tapering and what to expect during the process. When starting therapy agree on a plan for tapering and ceasing therapy that considers the individual, their medical history and psychological comorbidities, social supports, possible adverse effects and the patient's ability to self-manage. **For patients taking gabapentinoids long term**, consider a more gradual dose taper over 4–8 weeks; this enables observation for emergent symptoms that may have been controlled by the medicine, and may reduce withdrawal effects.	

Consider referral to or advice from a pain medicine or addiction specialist.

Box 2. Useful resources

Allied Health professionals:

- For information about **DVA funded services** and eligibility, go to: www.dva.gov.au/health-and-wellbeing/treatment-your-health-conditions
- For veterans and families counselling through **Open Arms**, go to: www.openarms.gov.au
- To find a **psychologist**, go to: www.psychology.org.au/Find-a-Psychologist
- To find a **physiotherapist**, go to: https://choose.physio/findaphysio
- To find an **exercise physiologist**, go to: www.essa.org.au/find-aep
- To find an **occupational therapist**, go to: www.otaus.com.au/find-an-ot

Chronic pain management:

- For more information on chronic pain management see the **Veterans' MATES topic: Understanding chronic pain**, at: www.veteransmates.net.au/topic-48-therapeutic-brief
- **Pain Management Network** provides information and resources for patients and health professionals including to aid the development of skills and knowledge in self-management, at: www.aci.health.nsw.gov.au/chronic-pain
- **Neuro Orthopaedic Institute (NOI)** has evidence-based multimedia resources for pain, at: www.noigroup.com
- **RACGP handbook of non-drug interventions (HANDI)** promotes effective non-drug treatments, at: www.racgp.org.au/clinical-resources/clinical-guidelines/handi/handi-interventions
- **painHEALTH** information assists patients with the management of pain, at: http://painhealth.csse.uwa.edu.au and paced activity, at: https://painhealth.csse.uwa.edu.au/pain-module/pacing-and-goal-setting
- **Painaustralia** has information on finding health services, at: www.painaustralia.org.au/pain-services
- **MindSpot** includes free online courses for patients (including an eight week CBT-based Pain Course on self-management), immediate strategies, screening assessment tools, and feedback via phone call, 1800 61 44 34, or email, at: https://mindspot.org.au/about-pain
- For information on **opioid-related harms**, recent strategies to help reduce the harms and further resources, go to: www.tga.gov.au/alert/prescription-opioids-hub

Full reference list available at: www.veteransmates.net.au

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