Indian Health Service
National Pharmacy and Therapeutics Committee
Calcium Channel Alpha-2-Delta Ligands
Use in Neuropathic Pain Management
NPTC Formulary Brief
May 2014

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the calcium channel alpha-2-delta ligands, gabapentin and pregabalin, and their place in the treatment of neuropathic pain at the May 2014 meeting. The NPTC last reviewed treatment of diabetic neuropathy in September 2010 and added gabapentin to the National Core Formulary based on evidence available at that time. Neuropathic pain is defined as pain resulting from a disturbance of the central or peripheral nervous system. The general prevalence of neuropathic pain is reported as 2 to 18%. Painful diabetic neuropathy (PDN) and postherpetic neuralgia (PHN) have prevalence rates of about 15%. Both gabapentin and pregabalin are FDA approved for treatment of PHN. Pregabalin is also FDA approved for treatment of diabetes associated and spinal cord injury associated neuropathic pain as well as for fibromyalgia. Gabapentin is not FDA approved for treatment of neuropathic pain; however, it is commonly used in the treatment of various types of neuropathic pain.

Discussion:
Publications from the British National Institute for Clinical Excellence (NICE), Cochrane Review Committee, the OHSU Drug Effectiveness Review Project, the Canadian Pain Society, the International Association for the Study of Pain, and the European Federation of Neurological Sciences were reviewed. Gabapentin and pregabalin were both shown to be effective in the treatment of neuropathic pain. A majority of the reviews looked specifically at diabetic neuropathy and post-herpetic neuralgia. In all of the guidelines, gabapentin and pregabalin, in addition to antidepressant (discussed separately), were recommended as first line agents in the treatment of neuropathic pain with the exception of trigeminal neuralgia. There was no preference as to which agent should be tried first. If one first line agent was ineffective, it was recommended to try a different first line agent.

Gabapentin exhibits nonlinear pharmacokinetics and as its dose is increased, bioavailability decreases and less drug is absorbed. It should be titrated up from a low starting dose until either analgesia is achieved or side effects experienced. Maximum recommended doses are 3600mg/day for PDN and 1800mg/day for PHN. Efficacy may be seen in as little as 2 weeks, but may take several months for an adequate therapeutic trial. Pregabalin has linear pharmacokinetics and requires a shorter titration period. It is not effective for PDN at a dose of 150mg/day. The maximum recommended dose of pregabalin is 300mg/day for PDN and 600mg/day for PHN. Both agents must be dose adjusted for renal insufficiency.

Data suggests that only between 1 in 10 and 1 in 4 will get $\geq$ 50% pain reduction with these agents. It is important for patients to be educated that these agents do not eliminate pain, but help to make it manageable and improve quality of life. Withdrawal of these agents secondary to adverse events was 11% for gabapentin and 18-28% for those taking pregabalin.

There is a need for more studies looking at the calcium channel alpha-2-delta ligands and their use in the many different types of neuropathic pain. Use of these agents in combination with other treatment options for neuropathic pain is an area that is lacking strong recommendations.

Findings:
The NPTC decided to take no action in regards to changing the National Core Formulary. This decision was primarily based on the lack of data recommending one of the calcium channel alpha-2-delta ligands over the other. Pregabalin is still under patent and significantly more costly than gabapentin. Pregabalin is a controlled substance which requires more inventory control than gabapentin. Thus, gabapentin remains on the NCF and pregabalin has not been added at this time.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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