CONNECTICUT MEDICAL ASSISTANCE PROGRAM
DEPARTMENT OF SOCIAL SERVICES
&
KEPRO
QUARTERLY NEWSLETTER

Hitting a Nerve with the Gabapentinoids

Neuropathic pain, defined as pain caused by a disease or lesion of the somatosensory nervous system, is estimated to affect 7-10% of the population.[1,2,3,4] The somatosensory system is associated with the perception of touch, pressure, pain, temperature, movement, and vibration.[1] Nerves all over the body sense any changes in these parameters and send signals to the spinal cord and brain for further interpretation.[1] Damage to the sensory nervous system can alter signals from the peripheral nerves to the spinal cord and brain changing the electrical properties of nerves in the periphery by altering ion channel expression, specifically sodium, calcium, and potassium channels, within affected nerves.[1] These changes in ion channel expression lead to a state of hyperexcitability between the peripheral and central nerves, contributing to a loss of inhibition and development of neuropathic pain.[1,2]

Contributing factors or disease states associated with the development of neuropathic pain include older age, diabetic neuropathy, cancer, adverse effects of chemotherapy, post herpetic neuralgia, infectious disease (HIV, leprosy), trigeminal neuralgia, amputation, stroke, multiple sclerosis, Guillain-Barre syndrome, and inflammatory disorders.[1,2] Symptoms of neuropathic pain can include but are not limited to burning, tingling, sensitivity to touch, heat or cold, numbness, stocking / glove syndrome, squeezing, pressure, muscle spasm, and electric shock like pain. Neuropathic pain can lead to a decline in quality of life, physical and mental health (insomnia, anxiety, and depression), and social function. This can lead to polypharmacy while seeking pain relief through the use of multiple prescribers to obtain medications.[1]

The diagnosis of neuropathic pain takes into consideration the four criteria below.[2,5] A definitive diagnosis of neuropathic pain can be made if a patient meets all four criteria while a diagnosis of probable neuropathic pain can be made if a patient meets criteria one and two.[2,5]

1. Pain with a distinct neuroanatomical distribution
2. A medical history that suggests a lesion or disease of the nervous system
3. A confirmatory test to demonstrate neuroanatomical distribution
4. A confirmatory test to demonstrate a lesion or disease of the nervous system

Traditional treatment of neuropathic pain focuses primarily on treating the symptoms rather than the cause, because once neuropathic pain occurs, it can rarely be reversed. Analgesics such as acetaminophen, NSAIDs and opioids typically have little to no effect on neuropathic pain. First line agents include the gabapentinoids (gabapentin and pregabalin), duloxetine (serotonin norepinephrine reuptake inhibitor), and certain tricyclic antidepressants such as desipramine.[6] Second and third line agents include tramadol and tapentadol.[2,6] Opioids that are NMDA receptor antagonists (buprenorphine and methadone) may be tried for neuropathic pain. Alternative treatment options include capsaicin patches, lidocaine patches, and botulinum toxin A.[2,6] Non-pharmacologic treatments such as physical therapy, cognitive behavioral therapy, improved patient mood, reduced disability, and setting realistic expectations, can cause pain reduction. While certain contributing factors cannot be averted, measures such as leading a healthy lifestyle, receiving the herpes zoster vaccine and appropriately managing disease states such as diabetes or HIV, can act as preventative measures.

Gabapentinoids are considered first line options for the treatment of neuropathic pain, however, there are still many unknowns about this class of medication including appropriate indications, exact

Table 1. Gabapentinoid FDA Approved Indications

Gabapentin	Pregabalin	Pregabalin CR
♦ Post herpetic neuralgia ♦ Epilepsy with partial onset seizures	♦ Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) ♦ Management of post herpetic neuralgia ♦ Adjunctive therapy for the treatment of partial onset seizures in patients 1 month of age and older ♦ Management of fibromyalgia ♦ Management of neuropathic pain associated with spinal cord injury	♦ Neuropathic pain associated with diabetic peripheral neuropathy (DPN) ♦ Post herpetic neuralgia (PHN)

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mechanism of action, and abuse potential. For the purpose of this article, we will focus on the gabapentinoids.

Gabapentin was first approved by the FDA in 1993 as an adjuvant for the treatment of partial seizures with an indication for treatment of post herpetic neuralgia added in 2004. Pregabalin was approved by the FDA in 2004 for the adjuvant treatment of partial seizures and for the treatment of neuropathic pain. (Table 1[7,8])

It is estimated that 4% of the US population currently use gabapentin or pregabalin with prescriptions increasing by 64% from 2012 to 2016.[9,10] During 2020, approximately 5% of the Connecticut Medical Assistance Program population received a prescription for a gabapentinoid. Utilization data specific for the CT Medical Assistance Program can be found in **Graph 1**. It should be noted that, since 2017 gabapentin falls in the top 5 medications prescribed (by prescription count) annually to CT Medicaid patients.

Contributing factors to the rise in prescribing of gabapentinoids is multifactorial and includes repercussions from the opioid epidemic, marketing practices, and an increase in off-label prescribing, all of which are interconnected. Due to the opioid epidemic, there have been more stringent regulations and restrictions placed on prescribing opioids for non-cancer chronic pain, leaving patients and prescribers to seek out non-opioid medications for pain control.[9] The gabapentinoids are seemingly less addictive and possess better safety profiles compared to opioids which can make gabapentinoids attractive alternatives to opioids for the treatment of neuropathic pain.[9] Marketing practices which led to an increase in the off label prescribing of gabapentinoids overlapped with the opioid epidemic. From 1995 – 2004, sale and utilization of Neurontin skyrocketed. During this time, lawsuits were brought against Pfizer, Inc., and Parke-Davis, a subsidiary of Warner-Lambert Company, for the illegal promotion of Neurontin for non-FDA approved indications which resulted in a guilty plea in 2004 .[11,12] During that same year, Neurontin went generic and Pfizer launched Lyrica with a broader range of FDA approved indications.[12] During 2012, a lawsuit was settled for inappropriate or misleading promotion of Lyrica for non-FDA approved indications.[13] While practitioners have autonomy to prescribe any medication off label, there was illegal marketing performed to increase the prescribing of these medications for non-FDA approved indications. Gabapentinoids are approved to treat seizures, neuropathic pain, and a narrow list of other pain indications. However, efficacy is lacking for uses such as non-neuropathic pain, anxiety, agitation, mood stabilization, treatment of alcohol withdrawal, and pre/post-surgical pain.[9,14] More than half of patients treated with gabapentinoids for neuropathic pain do not experience symptom relief.[15] When used off label, these medications are even less efficacious. Despite the paucity of evidence to support off label use, gabapentin and pregabalin have become two of the most widely used medications over the past decade.

Two types of calcium channels exist in humans – voltage gated calcium channels (VGCCs) and ligand gated (receptor gated) calcium channels.[16] Gabapentinoids are thought to exert their pharmacological effect by binding to the $\alpha_2\delta$ subunit of VGCCs, causing a decrease in central sensitization and excitability of neurons.[1,17] While there are 4 types of $\alpha_2\delta$ subunits ($\alpha_2\delta$-1, $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4), the gabapentinoids primarily bind to the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits.[16] The $\alpha_2\delta$-1 subunit plays a crucial role in the development of neuropathic pain and is found in skeletal, smooth, and cardiac muscle as well as within the Central Nervous System (CNS) and peripheral nerves.[2] The $\alpha_2\delta$-2 subunit is primarily found in the CNS.[16] While the exact mechanism by which the gabapentinoids exert their pharmacological effect is not completely understood, it is thought that binding to the $\alpha_2\delta$ subunits inhibits the release of excitatory neurotransmitters caused by ion channel changes and hyperexcitability of the somatosensory system, thus alleviating neuropathic pain, producing anticonvulsant activity, and exerting anxiolytic and sedative/hypnotic effects.[18,19]

The gabapentinoids were designed and developed to resemble the inhibitory neurotransmitter gamma aminobutyric acid (GABA) with the intent for these medications to possess GABAergic effects.[20] While they are structurally similar to GABA, the gabapentinoids do not bind to or have activity at GABA receptors, but still possess the ability to inhibit excitatory neurotransmitters through their proposed

Graph 1. Connecticut Medical Assistance Program Unique Recipients and Prescription Count of Gabapentinoids Dispensed to the Connectict Medical Assistance Program Population

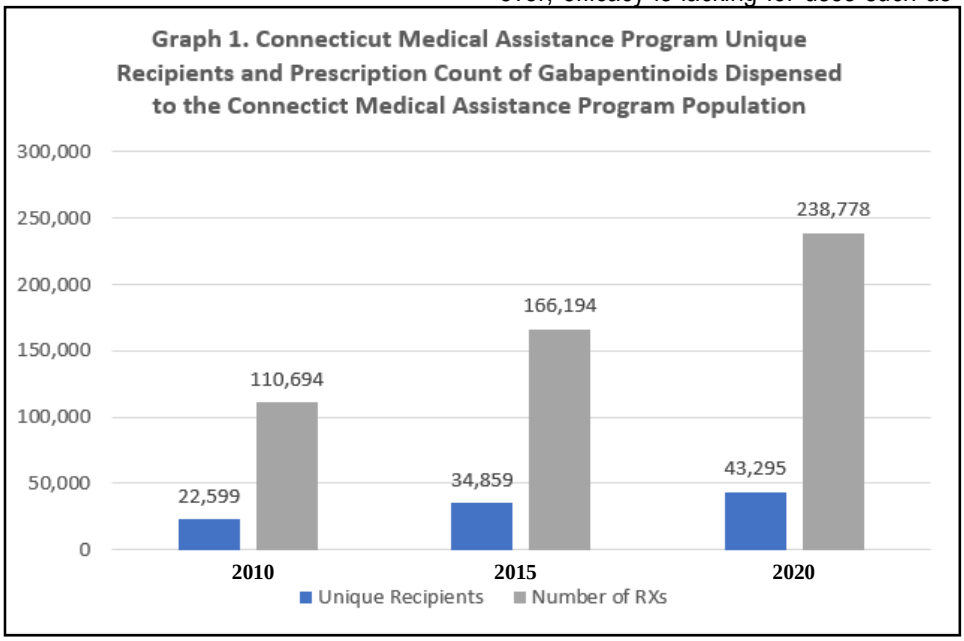

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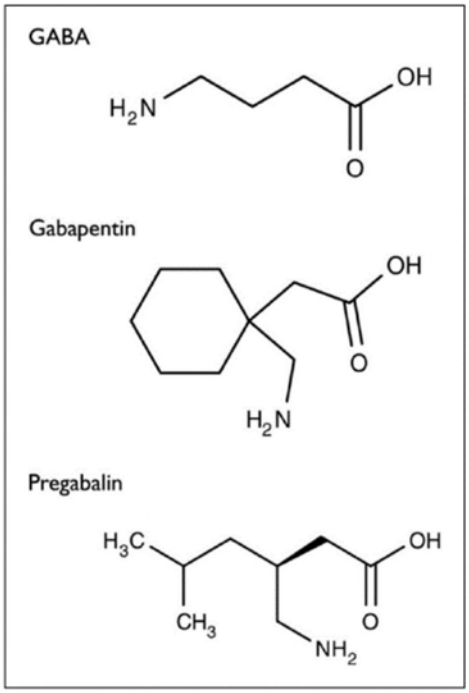
Image 1[18]



mechanism of action. The chemical structure of gabapentin contains a GABA molecule plus a lipophilic cyclohexane ring which was added during development to increase its bioavailability.[21] The chemical structure of pregabalin contains a GABA molecule plus isobutane which may have further increased the compound's bioavailability even more so than gabapentin.[18] (Image 1)

The gabapentinoids are associated with side effects such as ataxia, drowsiness, edema, fatigue and myoclonus. Approximately one third of patients report experiencing dizziness and somnolence with both medications carrying a warning for these effects.[7,8,22] Moderate weight gain and GI side effects such as dry mouth, constipation, and nausea can occur with the gabapentinoids.[21] Both medications carry additional warnings or precautions for respiratory depression, angioedema, suicidal ideation, and risk of withdrawal upon abrupt discontinuation. The recommended maximum dose of gabapentin for neuropathic pain is 3600 mg/day, with no clinical benefit reported at doses above 1,800 mg/day. The recommended maximum dose of pregabalin for neuropathic pain ranges from 300 - 600 mg/day depending on the type of neuropathic pain being treated.[7,8,21]

Pregabalin has a faster onset of action, greater potency, and greater binding capacity compared to gabapentin.[17,21-23] A general principle to follow when considering dose is that 50 mg of pregabalin is roughly equivalent to 300mg of gabapentin. Absorption of gabapentin occurs in the small intestine with a 30-60% oral bioavailability that follows zero order saturable absorption, meaning the greater the dose given the less absorption that occurs after the saturation point.[17,21,22] Pregabalin is absorbed in the small intestine and the proximal colon with a 90% bioavailability that follows linear absorption, meaning regardless of dose, approximately 90% of pregabalin administered will be absorbed.[17,21,22] Patients who undergo a Roux-en-Y gastric bypass or ileostomy may benefit from liquid preparations of either medication due to the effect these procedures have on medication absorption.[24] Conversely, it has been reported that gabapentin exposure increases by 44% after morphine administration which is thought to be due to morphine induced lower GI motility, providing more time in the small intestine for gabapentin to be absorbed.[25] This concept can be extrapolated to all opioids.

Gabapentin and pregabalin have minimal drug interactions due to bypassing hepatic metabolism and lack of reliance on the cytochrome P450 system.[22] Both drugs are renally eliminated with the majority excreted in the urine unchanged.[22] Dose reduction is required in renal impairment with dosing recommendations listed in **Table 2.**[17] Patients on hemodialysis should receive the dose recommended for their individual creatinine clearance, however, on dialysis days should receive a supplemental post-dialysis dose to augment what was cleared during dialysis treatment. If dosing is not adjusted for renal impairment, gabapentinoid toxicity can occur. Patients may present with an increase in sedation, confusion, ataxia, gait disturbance, myoclonus, and tremor.[21] Dose adjustments should be made in patients who have chronic lung or renal impairment, especially when given with medications that can cause respiratory depression such as opioids or other CNS depressants.

The gabapentinoids can cause euphoric and psychedelic effects, dissociation, increased sociability, and relaxation. At therapeutic doses, approximately 1-12% of patients experience these effects,[22] however, when administered at supratherapeutic doses (gabapentin > 3600 mg/day or pregabalin > 600 mg/day), these effects occur at higher rates.[19,26,27] Gabapentinoids are misused by patients who want to change their state of consciousness or to get "high," to potentiate the effects of other medications such as opioids, to avoid detection of abused medications upon urine screens, or simply because

Table 2. Recommended Dose Adjustments in Renal Impairment

CLcr (creatinine clearance)	Recommended Max Dosing Gabapentin	Recommended Max Dosing Pregabalin
30-59 ml/min	700 mg BID	150 mg BID 100 mg TID
15-29 ml/min	700 mg QD	75 mg BID 50 mg TID
< 15 ml/min	300 mg QD	75 mg QD
Supplemental doses in hemodialysis	100-300 mg post dialysis	75-150 mg post dialysis

TID-three times a day, BID-twice a day, QD-once a day

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these medication are more accessible than other medications of abuse.[22,27] It has also been reported that patients use gabapentinoids to alleviate opioid withdrawal.[27]

Both gabapentin and pregabalin have a higher likelihood of abuse and misuse in patients who have a substance use disorder compared to those who do not, particularly opioid use disorder (OUD).[22,23,28] 40% of CT Medicaid patients who received gabapentinoids during 2020 had a co-occurring diagnosis of a substance use disorder and 25% received a concurrent opioid prescription. Additionally, it should be noted that pregabalin has a higher abuse potential compared to gabapentin that is thought to be due it's higher potency, faster absorption, and linear pharmacokinetics.[29-31] While pregabalin is classified as a schedule V controlled substance, gabapentin is not scheduled. Despite this, certain states consider gabapentin a controlled substance (AL, KY, MI, ND, TN, VA, and WV) and other states have mandated that gabapentin prescriptions be reported to their prescription drug monitoring programs (CT, DC, IN, KS, MA, MN, NE, NJ, OH, OR, UT, and WY).[32]

In addition to the risk of abuse and misuse, the gabapentinoids can cause withdrawal. Larger doses and longer length of treatment directly correlate with withdrawal symptoms upon abrupt discontinuation. Symptoms are similar to benzodiazepine withdrawal and can include irritability, dysphoria, tremor, seizure, insomnia, and tachycardia.[23] Tapering is recommended to negate withdrawal effects. Because abrupt discontinuation of gabapentinoids can cause withdrawal, they are viewed as being capable of causing physical dependence.[26]

When used alone, gabapentinoids carry a low risk of causing fatal overdose, however, when used in conjunction with other CNS depressants (benzodiazepines, opioids, alcohol), the risk of respiratory depression, overdose, and death is potentiated.[26,29] Gomes, et al reported an odds ratio of an opioid related death to be 49% higher in patients exposed to gabapentin and opioids when compared to opioids used alone.[25] In December 2019, the FDA issued a drug safety communication warning about the serious breathing difficulties that may occur in patients using gabapentin or pregabalin who also have respiratory risk factors defined as the use of opioids and other CNS depressants, respiratory conditions such as COPD, and older age.[33]

These risks coupled with gabapentinoid utilization in patients with renal impairment within the Connecticut Medical Assistance Program population, spurred the DUR Board to develop educational communication to prescribers within the State. Prescribers whose patients are receiving greater than the maximum recommended dose of a gabapentinoid for their renal impairment diagnosis (Stage IV to ESRD) who are also receiving either a CNS depressant (opioid or benzodiazepine) or who have a respiratory disease, will be notified via a drug utilization review letter during January 2022. In presenting this information, it is recognized that the management of each patient's drug therapy depends upon assessment of the entire clinical picture. Although there are risks associated with gabapentin and pregabalin, they do have a place in the treatment of neuropathic pain and can provide benefit in the appropriate situation.

While gabapentinoids have a legitimate place in therapy, it is important to keep in mind that they are less than 50% effective at alleviating neuropathic pain. Physical therapy, cognitive behavioral therapy, and working to mitigate pain rather than complete elimination require effort by the patient such as setting realistic pain goals; providing continuity of care and follow-up require prescriber effort. Working together to mitigate pain, set achievable goals, and utilizing alternative therapeutic approaches may be effective treatment strategies for neuropathic pain.[34] If gabapentinoid use is deemed appropriate, pharmacovigilance is paramount. Safety evaluations should be conducted to identify patients at risk of gabapentinoid abuse; specifically those patients receiving concurrent CNS depressants which increase the risk of overdose. Regular assessment of respiratory and renal function as well as pain control and symptom relief must be considered. If there is little or no pain relief after a trial period, the gabapentinoid should be discontinued using a taper schedule to avoid withdrawal. Neuropathic pain can have an effect on all aspects of life. Careful consideration for use and appropriate utilization of medications indicated for this disease is of utmost importance.

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