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RESEARCH ARTICLE

Gabapentin—Friend or foe?

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Abstract

Background: Gabapentin is a recommended first-line agent for treating neuropathic pain; however, its efficacy rate is reportedly low, and the risk of adverse events is high. A plausible explanation for this lies with its wide range of actions, the entirety of which have yet to be fully elucidated.

Methods: A review of the literature was conducted on gabapentin's known and proposed analgesic mechanisms of action, as well as potentially opposing or detrimental actions.

Results: Gabapentin's classical analgesic mechanisms involve direct attenuation of excitatory neurotransmission in the spinal cord via inhibition of neuronal ion channels, while indirect mechanisms include descending inhibition and block of injury-evoked synaptogenesis. Glial effects have also been reported; however, whether they are neuroprotective or detrimental is unknown. Furthermore, data from animal models do not reflect clinical outcomes.

Conclusions: Gabapentin's clinical use should be reconsidered according to the net effects of its numerous assumed actions, including the tripartite synapse and oligodendrocyte effects. Whether it is doing more harm than good, especially in the scenarios of incomplete or loss of response, warrants consideration when prescribing gabapentin.

KEYWORDS
analgesia, gabapentin, glial cells, neuropathic pain, pharmacologic actions

INTRODUCTION

Gabapentin and pregabalin have a long history of use in treating neuropathic pain, having been approved by the Food and Drug Administration (FDA) in 2002 and 2004, respectively, for the indication of neuropathic pain associated with postherpetic neuralgia (PDN; both) and diabetic peripheral neuropathy (DPN; pregabalin only). A large portion of their use, however, is off-label.[1] In addition, recognition of the opioid crisis and a significant reduction in opioid prescribing has contributed to substitution with gabapentinoids for the management of non-neuropathic pain,[2,3] yet there is no clear evidence that this is a medically effective policy. We and others have been concerned with this increasing occurrence. It is also becoming increasingly clear that there is a significant side effect profile that extends beyond the typical symptoms (such as dry mouth, nausea, and altered bowel function) and there is decreased safety when combined with other drugs, particularly benzodiazepines and opioids.[4–6] There are also concerns around altered behavior, abuse, misuse, and diversion.[4,7]

Importantly, gabapentinoids may not be as effective as initially thought,[8] and there has been little discussion as to why the response rate for major neuropathic pain relief is rather low. This prompted us to review gabapentin's mechanisms of action to understand its specific role more definitively, where it should be

prescribed, and any potential inadvertent effects that may require review and termination of prescription. The aim of this commentary is to provide the reader with a comprehensive understanding and assist clinicians in choosing the right patient with the right condition for therapy.

Evidence for neuropathic pain

The first case reports of treatment of refractory neuropathic pain conditions with gabapentin were presented in 1996.[9,10] In 1998, confirmatory evidence was published for treatment of PHN,[11] for which it received FDA approval, as well as DPN.[12] The efficacy of pregabalin was demonstrated in several trials, gaining it approval for both indications.[13] Concerningly, the latest Cochrane review of gabapentin showed that the Numbers Needed to Treat for major pain relief (>50%) are worsening over time (6.9 for PHN and 5.9 for DPN) and concluded that <50% of patients treated will not derive meaningful pain relief but will likely experience adverse events.[8,14] Evidence for other neuropathic pain conditions is limited and there is insufficient data to support use in unapproved pain conditions, such as chronic low back pain and sciatica.[15,16]

Excessive Off-label prescription

Gabapentinoid use more than tripled in the USA between 2002 and 2015 and continues to rise.[3,17] Excessive off-label prescribing has been a major contributor. An investigation of prescribing practices in the USA found that 83% of gabapentin prescribing was off-label.[18] This has been driven partly by alleged aggressive promotion of off-label use for pain by the manufacturer, and biased reporting of questionable trials for off-label use.[2,19,20] Gabapentinoids have also become popular alternatives to opioids for pain and are widely recommended as first-line agents for the treatment of neuropathic pain, despite limited supporting evidence and safety concerns.[2,3,21]

Gabapentinoids in fatal opioid overdosage

Of major concern is an increase in prescriptions observed for patients co-prescribed opioids and/or benzodiazepines.[17] Concomitant use with opioids significantly increases the risk of fatal opioid overdose, especially at high gabapentin doses, likely due to exacerbated respiratory depression.[6] A study of accidental mixed drug fatalities involving opioids found gabapentin to be present in 26% of cases and typically within normal therapeutic dose ranges.[22]

Incidence in prescription drug monitoring programs

Excessive off-label prescribing and accumulating evidence of misuse and abuse prompted reclassification of gabapentinoids as controlled substances in the UK.[4,7] In the USA, only pregabalin is a federally controlled substance, whereas gabapentin has been reclassified in several states, while other states have implemented mandatory prescription drug monitoring programs.[7] In Australia, accumulating reports of misuse, abuse and dependence saw boxed warnings added to gabapentinoid-containing products.[23] As of 21 February 2022, the database of adverse event notifications included 221 related deaths, 36 reports of dependence, 21 reports of abuse and 13 reports of misuse.[24]

METHODS

The PubMed database was searched for relevant articles between Jan 1, 2010 and Jun 22, 2021. PubMed search terms included: "gabapentin* AND pain"; "gabapentin* AND (voltage-gated calcium channel*)"; "gabapentin* AND (descending inhibition)"; "gabapentin* AND (potassium channel)"; "gabapentin* AND (*glia* OR oligodendrocyte OR astrocyte)"; "oligodendrocyte AND AMPA; oligodendrocyte AND cannab*". The [Title/Abstract] field designation was used, and results were filtered for English language. Additional articles were identified from the "Similar articles" linked to PubMed search results and from references within relevant articles.

RESULTS

Analgesic mechanisms of action

Voltage-gated Ca^{2+} channel inhibition

Initially, it was shown that gabapentin acted on neuronal voltage-gated Ca^{2+} channels (VGCCs), which we now know occurs via the auxiliary α2δ subunit, resulting in decreased presynaptic release of excitatory neurotransmitters.[25] The α2δ-1 subunit is heavily expressed in dorsal root ganglion (DRG) and spinal dorsal horn and is significantly upregulated following nerve injury and correlates with allodynia.[26] This key role in neuropathic pain provides a mechanistic rationale for clinical use.[26–29] Gabapentin also binds to the α2δ-2 subunit, though this is believed to have little analgesic effect.[30] α2δ-2 is highly expressed in cerebellum and brainstem,[27] and interaction with gabapentin has been shown to promote corticospinal plasticity and regeneration in mice after spinal cord injury.[31] Data suggest that α2δ-1 is

mainly expressed in glutamatergic (excitatory) neurons, while α2δ-2 is predominantly expressed in inhibitory GABAergic interneurons and cholinergic interneurons.[27] Whilst gabapentin also attenuates neurotransmission to inhibitory neurons, preferential inhibition of excitatory neurons has been demonstrated in the substantia gelatinosa of the dorsal horn.[32]

NMDAR complex inhibition

A more recent study challenged the early belief that VGCCs are the critical targets of gabapentin, instead, demonstrating that gabapentin reduces neuropathic pain by interrupting the formation of hyperactive α2δ-1- N-Methyl-D-Aspartate-type glutamate receptor (NMDAR) complexes.[28] NMDARs play a key role in synaptic plasticity and neuropathic pain, and interaction with α2δ-1 has been shown to cause increased synaptic activity in the dorsal horn after nerve injury.[33]

Other actions

The literature also highlights several other actions with the potential to aid or antagonize gabapentin's analgesic efficacy.

Thrombospondin inhibition

Gabapentin has also been shown to inhibit astrocyte-derived thrombospondins (TSPs). TSPs are released in response to stimuli from damaged cells to induce the formation of new synapses and therefore play a major role in chronic pain after neuronal injury by increasing excitatory synapses and the rate of excitatory synaptic currents.[34,35] TSP4 is upregulated in DRG after central and peripheral nerve injury and is correlated with increased excitatory presynaptic input and chronic pain development.[35,36] Gabapentin inhibits TSPs via α2δ-1 to block developmental and injury-evoked synaptogenesis.[34,37] Depending on the postsynaptic target, analgesia may be enhanced if synaptogenesis is inhibited on excitatory neurons or reduced if the synaptogenesis is inhibited on inhibitory populations, effectively compromising inhibitory gating in these circuits. Furthermore, block of TSP4-α2δ-1 only occurs if gabapentin is administered early during the establishment of neuropathic dysfunction, with delayed treatment having no effect.[37]

Modulation of HCN Channels

Gabapentin has also been shown to affect hyperpolarization-activated current (I_h) by modulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channels regulate neuronal excitability by modulating resting membrane potential, lowering membrane resistance, and reducing synaptic inputs, and can have excitatory or inhibitory effects.[38] In rat hippocampal slices, gabapentin increased I_h in pyramidal[39] and inhibitory[40] neurons, possibly representing a protective mechanism against excessive neuronal activity. In contrast, in mouse dorsal horn, gabapentin reduced I_h in inhibitory neurons via HCN4 modulation.[41] Dysregulation of HCN1, 2, and 3, and enhanced I_h have been implicated in neuropathic pain, while involvement of HCN4 and the effect of gabapentin on this subunit is unknown.[42] Depending on the conditions, subtype, and neuronal target, block of HCN channels could reduce inhibitory neuron activity or reduce synaptic input from inhibitory neurons, and therefore has the potential to compromise spinal inhibition and exacerbate pain.

Glial effects

Several preclinical studies have demonstrated secondary effects on glial cells in the spinal cord and brainstem. An important point from these findings is the active role that glia play in neuronal processing mechanisms and the potential for glia to be affected by gabapentin. Thus, reframing the simple view of neuron-to-neuron signaling in the nervous system to acknowledge the critical role of neuronal–-glia interactions (a tripartite model of neuron–neuron–glial cell) is important for a more complete appreciation of gabapentin's actions in neuropathic pain.[43–45]

Astroglial activation

Beyond the spinal cord, a role for gabapentin in increasing descending noradrenergic inhibition in the locus coeruleus has been demonstrated.[46] Gabapentin blocks presynaptic GABA release (via α2δ-1 inhibition) and activates astrocytic glutamate transporter 1 (GLT-1) to promote presynaptic glutamate release to noradrenergic neurons, therefore suppressing pain transmission in the spinal cord.[46] Importantly, this analgesic mechanism is impaired in a chronic neuropathic pain state, and gabapentin's efficacy is lost over time because of astroglial glutamate dysregulation due to downregulation of GLT-1, which is seen weeks after nerve injury in rats.[46,47] This was overcome by restoration of GLT-1 expression with sodium valproate, an inhibitor of histone deacetylase.[47]

Microglial actions

Pathological microglial activation and release of pro-inflammatory factors after nerve injury is well-documented in neuropathic pain.[48] Rodent pain model

studies have shown that gabapentin's anti-allodynic and anti-hyperalgesic effects may involve inhibition of microglial activation, but not astrocytes, in the dorsal horn.[49–51] Concerningly, microglial play important neuroprotective roles, such as anti-inflammatory cytokine production and regulation of astrogliosis.[48] Recently, gabapentin was found to stimulate microglial production of interleukin-10 (anti-inflammatory) and subsequent expression of ß-endorphin in a rat model of neuropathic pain.[52] Whether the protective or negative effects translate to patients remains to be determined.

Oligodendrocyte effects

Oligodendrocytes are critical for effective neural transmission by supporting action potential discharge, and it is important to consider the potential detrimental effects of pharmacological agents on axons and oligodendrocytes to obtain a more complete view of how drugs modify signaling in neurons and circuits.[53] For example, mitigating the potential rise of extracellular potassium concentrations during rapid neuronal firing, could inhibit further potassium efflux and impair neural transmission. Glial cells, especially astrocytes and oligodendrocytes, are critical in preventing such impairment by pumping potassium intracellularly and sodium extracellularly, thus maintaining optimal ionic gradients for neuronal transmission.[54,55] In addition, the primary role of oligodendrocytes in myelination and myelin maintenance to increase axon conductance is of relevance to potential drug actions,[45] as is myelin remodeling to promote synaptic plasticity,[56] and metabolically supporting axons to meet the high energy demands of sustained action potential firing.[57] Thus, oligodendrocytes contribute to maintaining axon health, action potential propagation, and regulation of synaptic activity and neural circuits.

Healthy oligodendrocyte development and myelination require Ca^{2+} influx and regulation by L- and P/Q-type VGCCs and AMPARs, and possibly also NMDARs, and Ca^{2+} dysregulation can lead to severe pathological outcomes.[58] Gabapentin inhibits P/Q-type VGCCs in the dorsal horn and P/Q- and L-type VGCCs in the cerebral cortex.[59–61] Concerningly, blockade of Ca^{2+} influx via L-channel inhibition has been shown to significantly inhibit differentiation and maturation of oligodendrocyte progenitor cells and is associated with a decrease in myelinated axons.[62] Thus, gabapentin could potentially contribute to Ca^{2+} dysregulation in oligodendrocytes and axons. Interestingly, in a rat seizure model, chronic gabapentin treatment increased the number of degenerating hippocampal neurons.[63] In contrast, in a rat chronic sciatic nerve constriction study, gabapentin appeared to protect or restore sciatic nerve morphology via myelin preservation or remyelination; however, gabapentin was administered pre-injury, and improvements in neuropathic pain symptoms were lost or reduced after 15 days of treatment.[64]

DISCUSSION

Looking beyond the classical mechanism of gabapentin on α2δ subunits at the primary afferent synapse, gabapentin's net effect will also reflect actions on other sites, such as HCN4 channels, and possible beneficial and/or detrimental glial cell effects. Together, this expanded view may help explain the overall low efficacy in neuropathic pain, and why analgesic efficacy may be lost over time.

Preclinical versus clinical effects

It is important to note that the majority of data has come from animal models and does not reflect the variable but mostly low rates of efficacy seen in humans.[65] This was highlighted by a randomized controlled trial of intrathecal gabapentin in a group of mostly mixed and neuropathic pain patients, in which no meaningful analgesic benefits were found despite positive preclinical results.[66] The authors suggested a re-evaluation of gabapentin's proposed analgesic mechanism of action in humans. The results of this and other studies suggest that supraspinal actions of gabapentin, such as engagement of cortical endogenous opioid pathways and dopamine neurotransmission to treat affective and motivational aspects of persistent pain, may be necessary for analgesia in humans.[67]

Additionally, the paradox of rapid analgesia in animal injury models yet delayed/small effects in patients has been discussed and warrants further investigation.[68] This is thought to be related to the level and time course of α2δ-1 expression. In nerve injury models, α2δ-1 is significantly upregulated following injury and correlates with rapid gabapentin effects, while in uninjured animals/nerves, acute effects are absent or delayed.[68] In spinal nerve-injured rats, gabapentin had a significantly higher inhibitory effect on injured DRG neurons with increased N-type VGCC expression compared to uninjured neurons, possibly a result of α2δ-1 abundance.[69] Also in the spinal nerve injury model, α2δ-1 levels were shown to peak around 2–4 weeks and gradually declined to near baseline levels over the next 5–20 weeks.[29] In a rat central post-stroke pain model, long-term gabapentin insensitivity was associated with decreased α2δ-1 expression in thalamic neurons 3-weeks post-injury.[70] This data supports the idea that α2δ-1 is a key player in the development of neuropathic pain in injured neurons but may be less important in the maintenance of neuropathic pain. If the same time

course of acute high α2δ-1 expression post-injury followed by a return to normal expression is seen in humans, this could explain why gabapentin has such a low efficacy rate in patients with chronic neuropathic pain and/or loses efficacy with long-term use.[68] Likewise, if the difference between α2δ-1 and VGCC density and preference between excitatory and inhibitory neurons is no longer significant, and the possible beneficial and detrimental glial effects are considered, the net effect of gabapentin may hypothetically be null.

Implications for treatment

Given the growing appreciation that gabapentin has numerous sites of action throughout the nervous system, there are several possible implications for prescribing. Scenarios that warrant consideration include:

1. If gabapentin is found to be effective for persistent neuropathic pain and long-term prescription is being considered, then a careful clinical (history and examination) follow-up and review should occur to ensure no worsening of neurological function.
2. If gabapentin is found to be ineffective for persistent neuropathic pain, then consideration should be given to replacing gabapentin with alternative treatments.
3. In the setting of incomplete or loss of gabapentin response, a second agent could be added to restore response, such as sodium valproate[46] (note: clinical data have not been gathered for this approach).
4. In the setting of clear loss of gabapentin efficacy, gabapentin could be ceased, and alternative agents that have the potential to address any gabapentin-induced functional impairment (eg: oligodendrocytes) and improve neuropathic pain symptoms could be considered. For example, there is great interest in targeting the endocannabinoid system for analgesia, and endocannabinoid signaling has demonstrated roles in oligodendrocyte health and disease.[71,72] Further research is warranted.

CONCLUSION

Gabapentin's effects should be considered according to the net effects of several potential sites of action, including the tripartite connection of neuron/synapse/neuron and glial cells, especially oligodendrocytes. Its effect may be positive or negative, and sustained or temporary, depending on the interaction with a variety of receptors and cell types. We caution against leaving patients with high neuropathic pain levels on long-term gabapentin as more harm than good may be occurring. Further work is necessary to understand where a long-term prescription is warranted and where it is not.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in this review.

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