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Review Article

Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review

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Abstract

The focus of perioperative pain management should be to attempt to minimise the nociceptive input and reduce the risk of transition to central sensitisation. Gabapentinoids are being increasingly used as adjuncts for management of perioperative pain. Although gabapentinoids are classed as calcium channel blockers, their mechanisms of action are poorly understood. The analgesic effect in neuropathic pain is well evidenced but the role in postoperative pain is less certain. Medline and EMBASE database searches were conducted to identify studies relating to mechanisms of action and effects in experimental animal models of inflammatory and postoperative pain and human models of experimental pain. The effects of gabapentinoids may be attributed to depression of dorsal horn sensitivity through a multitude of mechanisms. They inhibit calcium mediated neurotransmitter release through effects on α2δ-1 subunits. They inhibit forward trafficking of α2δ-1 from the dorsal root ganglion, their recycling from endosomal compartments, thrombospondin mediated processes and stimulate glutamate uptake by excitatory amino acid transporters. Mechanisms not directly related to neurotransmitter release at dorsal horn include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions, and influence on the affective component of pain. Gabapentinoids are effective analgesics in most animal models of inflammation and postoperative pain but effects in human models are variable.

Keywords: alpha 2-delta subunit 1 protein; gamma-aminobutyric acid; pregabalin

The gabapentinoids, pregabalin and gabapentin, have been the cornerstone of pharmacological management of neuropathic pain.[1] Despite the widespread use in neuropathic pain, the precise mechanism of action is uncertain. The effect of gabapentinoids in pain are assumed to be because of direct inhibition of voltage gated Ca^{2+} channels by binding to its α2δ-1 subunit resulting in reduction of presynaptic Ca^{2+} influx and subsequent release of excitatory neurotransmitters such as glutamate. This assumption is not correct as calcium currents are not consistently reduced by acute application of gabapentinoids.[2] Despite this, most studies show that gabapentinoids inhibit release of neurotransmitters in neuronal tissues.[2] This review explores the possible mechanisms by which gabapentinoids inhibit neurotransmitter release despite the lack of acute effect on Ca^{2+} currents. This review has also sought to identify the analgesic mechanisms unrelated to the direct inhibition of neurotransmitter release at the dorsal horn.

Although there is good evidence for the effect on neuropathic pain, the role in postoperative pain is less certain. Gabapentinoids are being increasingly used in the perioperative period as part of multimodal analgesia.[3] However, the

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Editor's key points

- The analgesic actions of gabapentinoids can be attributed primarily to blockade of voltage-gated calcium channels, but they have additionall targets as well.
- Gabapentinoids depress neuronal excitability through interactions with the α2δ-1 calcium channel subunit, stimulate descending inhibition, inhibit descending serotonergic facilitation, inhibit inflammatory mediators, and influence the affective component of pain.
- They are effective in animal models of inflammation and postoperative pain, but effects in human models of inflammation are variable.

evidence to support its use in postoperative pain is limited because of the poor quality of evidence from clinical trials.[4] This review sought to determine the effects of gabapentinoids in animal models of postoperative and inflammatory pain and in human pain models. The implications for clinical practice are discussed.

Methods

Medline and EMBASE database searches were conducted to identify studies relating to mechanisms of action and effects in experimental pain models (Appendix A). The reference lists of selected articles were explored for additional studies. Only manuscripts published in English were included. The level of evidence could not be graded as most studies were exploratory in nature. Various themes relating to mechanisms were identified and selected studies described.

Nociceptive pathways, voltage-gated calcium channels, and the α2δ subunit

Nociceptors are pseudo-unipolar: the cell bodies are located in the dorsal root ganglion (DRG), a single process bifurcates into a central axon that project to second-order neurons and local interneurons in the dorsal horn of the spinal cord, and a peripheral axon travels through the spinal nerve to the periphery.[5] After nerve injury or inflammation, the stimulation threshold of nociceptors is reduced. The sensitised nociceptors are activated by minimal stimuli—a process known as peripheral sensitisation that causes primary hyperalgesia. The action potentials that are transmitted to the nociceptors are relayed to the spinal dorsal horn through the central axon and to the periphery through the peripheral axon. This causes membrane depolarisation, activation of voltage-gated calcium channels (VGCCs) and calcium influx, triggering release of glutamate as a major neurotransmitter along with neuromodulators such as substance P, calcitonin gene-related peptide, and brain-derived neurotrophic factor. These are released both peripherally at the site of inflammation and in the dorsal horn, to produce an excitatory signal at the post synaptic targets.[5] The effects on the dorsal horn neurons of the spinal cord are mediated by the postsynaptic glutamate receptors—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate, *N*-methyl-D-aspartate and kainite.[6] Many neurons also regulate neurotransmitter release through expressing presynaptic glutamate receptors.[7] The excitatory interneurons in the dorsal horn are also glutamatergic. The enhanced release of glutamate in the dorsal horn of the spinal cord causes increased activation of postsynaptic nociceptive neurons resulting in central sensitisation and secondary hyperalgesia. The spinal cord is clearly an important site for modulation of central sensitisation, as it receives multiple inputs from peripheral neurons, interneurons, astrocytes, microglia, and descending modulatory controls.[8]

Generally, this process of sensitisation reverts back to normal after pain resolves with normal wound healing. However, persistent transmission of nociceptive signals leads to persistent central sensitisation through neuroplastic changes in the dorsal horn and higher centres, such as degeneration of inhibitory interneurons and remodelling of neuronal synapses by glial cells.[8]

Voltage-gated calcium channels

Voltage-gated and ligand-gated channels that are permeable to inorganic ions such as sodium, potassium, chloride, and calcium are essential for electrical activity of excitable cells such as neurons.[9] Calcium differs from the other ions as it also serves as an important signalling entity. Influx of calcium ions through high-voltage activated (HVA) calcium channels trigger a wide range of responses including gene transcription, neurotransmitter release, neurite outgrowth and activation of calcium dependent enzymes.[9]

VGCCs are comprised of multiple subunits: α_1, β, γ, and $\alpha_2\delta$ (Fig 1).[10] The α1subunit allows entry of calcium ions. It comprises four homologous domains (I–IV), each of which contain six transmembrane helices (S1–S6). The extracellular α_2 subunit is attached to the δ subunit via a disulfide linkage. The β subunit is entirely intracellular. VGCCs are classified into HVA (L-, P/Q-, N-, R-) and low-voltage activated (LVA; T-type) VGCCs.[11] Dorsal root ganglion cell bodies and presynaptic terminals that form synapses with dorsal horn neurons express increased density of N-type VGCCs.[10] The L-type channels are extensively found in both excitable and non-excitable tissues. Although less extensively studied, other subtypes may be involved in the pain pathway.[10]

α2δ subunit and pain

The auxiliary $\alpha_2\delta$ and β subunits have four isoforms and enhance the plasma membrane expression and function of HVA calcium channels but not LVA channels.[12] The α2δ-1 isoform that mediates the effects of gabapentinoids is present in the brain, skeletal, cardiac, and smooth muscle. α2δ-2 and α2δ-3 subunits are present in non-neuronal tissues in addition, whereas α2δ-4 is expressed in retinal neurons and other non-neuronal tissues.[12]

The α2δ-1 unit has widespread distribution in the mouse brain, especially in the cerebral cortex, hippocampus, and cerebellum.[12] Elevated concentration of α2δ-1 subunit is clearly associated with augmented pain processing. DRG neurons show increased expression after peripheral nerve damage in animal models of neuropathic pain.[13–16] The peak expression of $\alpha_2\delta$-1 occurs 7 days after injury and takes several months to decline, with a temporal relationship with the onset and resolution of evoked behaviours.[15] Deletion of α2δ-1 gene in mice models of neuropathic pain is associated with marked behavioural deficit in mechanical and cold sensitivity.[17] Intrathecal antisense oligonucleotides (synthetic polymers that can alter synthesis of specific proteins) complementary to a region in the α2δ-1 gene can reverse mechanical hypersensitivity in nerve ligation models.[14] The concentrations are elevated in the dorsal horn and mimic that of the DRG with decrease in concentrations and reversal of allodynia after

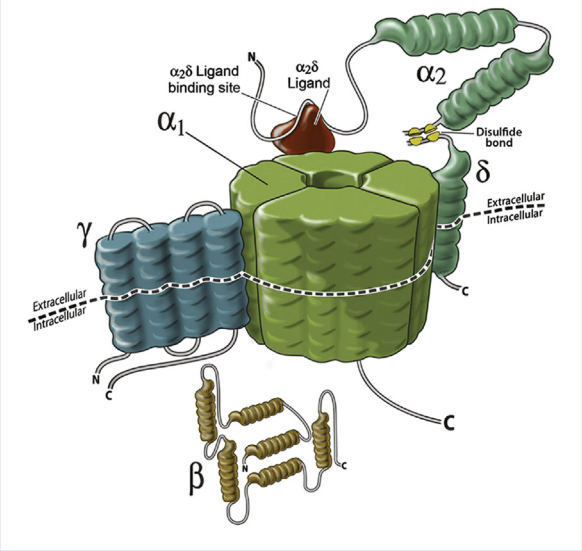

Fig 1. Voltage-gated calcium channels are composed of four subunits. The α1 subunit consists of four homologous domains, each containing six transmembrane segments. It is the pore-forming subunit. The β subunit is intracellular. The γ subunit has four transmembrane segments. The δ subunit has one transmembrane segment and is attached to the extracellular α2 subunit via a disulfide bond. Reprinted, with permission, from Elsevier.[10]

dorsal rhizotomy. This suggests that the elevated concentration of presynaptic α2δ-1 subunit in the dorsal horn is a result of transport by DRG neurons through their central axons.[14]

Increased concentrations of $\alpha_2\delta$-1 can cause neuropathic pain even in the absence of nerve damage. Transgenic mice that overexpress $\alpha_2\delta$-1 show symptoms of allodynia even when nerve damage is absent, which suggests that increased concentrations of $\alpha_2\delta$-1 are sufficient to cause neuropathic pain.[18] The frequency of miniature excitatory postsynaptic currents in the dorsal horn is increased and is reversed by intrathecally delivered antagonists of glutamate receptors.[19] This suggests that $\alpha_2\delta$ mediates spinal sensitisation by increased presynaptic glutamate release that enhances the sensitivity of postsynaptic neurons in the dorsal horn. However α2δ is not always associated with neuropathic pain as the upregulation of α2δ-1 is injury-specific with variable effects in animal models of neuropathic pain based on aetiology.[20]

Mechanism of action of gabapentinoids

Site of action

The actions of gabapentinoids are mainly at an intracellular site and require active uptake.[21] They were originally designed as γ aminobutyric acid (GABA) analogues but do not have any effects on GABA receptors. Gabapentin binds to $\alpha_2\delta$ receptors with greater affinity to the $\alpha_2\delta$-1 subtype.[22] Mutations of $\alpha_2\delta$-1 or $\alpha_2\delta$-2 block the neuronal actions of gabapentin by preventing its binding, but not mutations in $\alpha_2\delta$-3, indicating that the effects are mediated by $\alpha_2\delta$ subunits of VGCCs.[23] Several other sites of action have been described, such as NMDA receptors and sodium channels but the evidence is limited.[24–26] Although both drugs are absorbed by facilitated transport through system L-neutral amino acid transporters, pregabalin is rapidly and completely absorbed with peak plasma concentrations within 1 h as opposed to 3 h with gabapentin.[27] Unlike gabapentin, absorption of pregabalin is not saturable, with a linear pharmacokinetic profile and less variable bioavailability.[27] Although peak plasma concentrations of gabapentinoids are achieved within 1–3 h, peak cerebrospinal fluid (CSF) concentrations may take significantly longer, with a median time of 8 h.[28] They do not influence spinal neurotransmitter concentrations of glutamate, norepinephrine, substance P, and calcitonin gene-related peptide.[29] They are not metabolised by the liver and are excreted by the kidney with elimination half-lives of 6 h.[27]

Effect on DRG neurons

Gabapentinoids are considered to exert their effects by inhibition of calcium currents. There was modest inhibition of calcium currents in medium sized and isolectin B4 (IB4) negative DRG neurons (small sized neurons that express neuropeptides projecting to lamina I and II) after prolonged incubation.[30] The acute application of low concentrations of Mn^{2+}, which is a global VGCC blocker, was substantially more effective than gabapentinoids at inhibiting calcium currents in DRG neurons. If the classical mechanism is correct, Mn^{2+} should have been even more effective in suppressing synaptic transmission in the dorsal horn. However, the effectiveness was reversed in the dorsal horn. Gabapentinoids suppressed excitatory synaptic transmission in the substantia gelatinosa neurons, whereas Mn^{2+} had no effect. Clearly the moderate effect of gabapentinoids on calcium currents in DRG neurons alone could not explain its ability to reduce overall dorsal horn excitability. The reduction in neurotransmitter release because of gabapentin is therefore not entirely related to decreased calcium influx into presynaptic nerve terminals.

Gabapentinoids have anti-allodynic rather than anaesthetic effect as not all DRG neurons are sensitive to gabapentinoids.[30] They preferentially affect medium sized neurons associated with Aδ fibres that are often associated with nociceptive transmission and small IB4− neurons, with a complete lack of effect on the large and IB4+ neurons. Medium sized neurons and IB4− neurons project to excitatory neurons in the substantia gelatinosa, whereas large neurons associated with Aβ fibres and IB4+ neurons project to inhibitory neurons.[30]

Spontaneous firing of injured sensory neurons mediated by voltage-gated persistent sodium currents is implicated in the generation of neuropathic pain. Gabapentin decreased the amplitude of resonance and abolished the subthreshold membrane potential oscillations of A-type DRG neurons, in a chronic compressed dorsal root ganglion model.[25]

Effect on forward trafficking

The effects could be related to the forward trafficking of $\alpha_2\delta$ to neurotransmitter release sites. α2δ and β subunits could influence the HVA channel current density by increasing the expression of the pore forming α1 subunits. Gabapentinoids applied chronically could reduce calcium influx by suppressing the forward trafficking of $\alpha_2\delta$ and calcium channels to the plasma membrane.[13] This could explain the significant effects on dorsal horn excitability in spite of the moderate effects on DRG neurons. The prolonged duration required for gabapentinoid action *in vitro* can then be explained as a consequence of the time required to transport recently synthesised pore-

forming units to the terminals in the dorsal horn.[31] However, it is clear that decreased expression of HVA calcium channels at nerve terminals may not be relevant as their blockade by Mn^{2+} has very little effect on neurotransmitter release.[30,31]

Protein trafficking *in vivo* can be studied by obstructing trafficking by nerve section or ligation. The proteins that accumulate at the site of obstruction can then be studied. $\alpha_2\delta$-1 was found to accumulate proximal to the spinal nerve ligation (SNL) site but was not exclusively presynaptic. It was found in both the central and peripheral terminals, and this increased over the days after ligation, suggesting that they are transported to these terminals from their site of production in DRG cell bodies. Increased α2δ-1 concentrations in the dorsal horn are important for development of neuropathic pain. Chronic treatment of these spinal nerve ligated animals with pregabalin had a significant antiallodynic effect.[32] It reduced the accumulation of $\alpha_2\delta$-1 at the SNL site, in ascending DRG axons of the fasciculus gracilis and reduced the elevated concentrations of $\alpha_2\delta$-1 in the presynaptic terminals of DRG neurons in the spinal cord dorsal horn. However, it had no effect on the up-regulation of $\alpha_2\delta$-1 in DRG neurons. This indicates that the *in vivo* antiallodynic effects of chronic gabapentinoids are a result of inhibition of anterograde trafficking of $\alpha_2\delta$-1, thereby inhibiting neurotransmitter release.[32]

The reduction in forward trafficking of $\alpha_2\delta$ with gabapentin may be a consequence of inhibition of its Rab11-dependent recycling.[33] Rab11 is involved in the regulation of recycling of endocytosed proteins.[34] By inhibiting the recycling of α2δ in neurons, gabapentin might reduce the expression of plasma membrane calcium channels at presynaptic terminals. However, intrathecal administration of pregabalin had analgesic effects but did not inhibit the accumulation of $\alpha_2\delta$-1 at primary afferent terminals after peripheral nerve injury in rats.[35] This lack of $\alpha_2\delta$-1 accumulation may be a result of reduced drug concentrations at effect sites with intrathecal administration as compared with systemic administration.[35] The transport of α1:α2δ-1-subunit complexes to the cell surface is β-subunit dependent and can be influenced by gabapentinoid action on the β4a subtype.[36]

Effect on neurotransmitter release sites

α2δ increases the density of HVA calcium channels at release sites and promotes increased exocytosis. This enhanced effect is seen at decreased Ca^{2+} influx, indicating that elevated concentrations of α2δ allow synapses to make more efficient use of Ca^{2+} entry to drive neurotransmitter release.[37] Pregabalin actions were attenuated in knockout mice lacking the protein syntaxin 1A, a component of the synaptic vesicle release machinery, indicating that syntaxin 1A is required for pregabalin to exert its full presynaptic inhibitory effects.[38] The inhibitory effects can therefore be explained by the interruption of the ability of α2δ to facilitate interaction of HVA calcium channels with neurotransmitter release sites. The α2δ-mediated impaired synaptic transmission is attenuated by gabapentinoids.[39]

Effect on thrombospondin

Astrocytes are involved in many neuronal mechanisms, including the formation of new synapses.[40] Astrocyte-derived thrombospondins are involved in presynaptic plasticity through their actions on $\alpha_2\delta$-1, by binding to their von Willebrand factor domain.[40] Gabapentin can inhibit the formation of excitatory synapses by blocking the binding of thrombospondin to $\alpha_2\delta$-1.[41] It is unlikely, however, that the slow process of synaptogenesis contributes to the rapid effects of gabapentinoids. In contrast, gabapentin reversed neuropathic pain after intrathecal injection of thrombospondin-4 (TSP4) with return of withdrawal threshold to control concentrations within 24 h.[42] The rapid effects may be a result of interference with processes dependent on the interaction of TSP4 and calcium channels that may be key even before long-term changes such as synaptogenesis.[42] Increased TSP4 contributes to hypersensitivity by reduced expression of HVA and enhancing LVA in DRG neurons.[43]

Effect on descending serotonergic facilitation, descending inhibition and cortical mechanisms

Some of the analgesic effects are mediated through modulation of descending pathways. Increased descending serotonergic facilitation on spinal 5HT3 receptors is associated with the development of pain.[44–46] Antinociceptive effects of gabapentinoids were blocked by prior administration of serotonin receptor blockers and by selective ablation of superficial dorsal horn neurons expressing the neurokinin-1 receptor for substance P.[47–49] These neurons project to descending brainstem serotonergic pathways that increase spinal excitability. Activation of spinal 5-HT3 receptors in normal animals allowed gabapentin to inhibit neuronal responses where previously it was ineffective. Gabapentin induces glutamate release from astrocytes in the locus coeruleus that is the principal site of noradrenaline synthesis.[50] The analgesic effect of gabapentin in neuropathic pain in a rat SNL model was reduced because of downregulation of astroglial glutamate-1 transporter in the locus coeruleus that reduced spinal noradrenergic inhibition but was reversed by oral valproate that is an inhibitor of histone deacetylase.[51]

Gabapentinoid effects on the affective component of pain can explain some of the analgesic effects. Positron emission tomography imaging indicated that the analgesic effect is mediated by suppressing medial prefrontal cortex, a brain area involved in the affective response to pain, with extensive connections to the limbic system.[52] The supraspinal mechanisms that modulate the affective-motivational qualities of pain require engagement of cortical endogenous opioid circuits that activate mesolimbic reward system involved in motivational aspects of pain behaviour.[53]

Effect on glutamate transport

Glutamate released by excitatory stimulation can accumulate extracellularly and cause excitotoxicity. Its concentrations are regulated by rapid removal by excitatory amino acid transporters (EAATs).[54] The glial cells take up glutamate that is metabolised to glutamine by glutamine synthase and is transported back to the neurons to replenish glutamate at the presynaptic membrane.[54] The EAAT1 and EAAT2 subtypes are more widely distributed in the neuronal tissue and are responsible for most of the glutamate uptake, the reduced expression of which contributes to the development of neuropathic pain.[55] All subtypes are expressed in the dorsal horn post synaptic membranes.[56] EAAT3, however, is less abundant as compared with the other subtypes and may act by influencing glutamate metabolism rather than neurotransmission.[56,57] Pregabalin increased activity of EAAT3 in EAAT3-expressing oocytes in a dose-dependent manner, indicating that it may work by enhancing its trafficking to the plasma

Table 1 Analgesic mechanisms of gabapentinoids. HVA, high-voltage activated; DRG, dorsal root ganglion; EPSC, excitatory postsynaptic current; TTX, tetradotoxin; SNL, spinal nerve ligation; BBS, bungarotoxin binding site; eEPSC, evoked EPSC; mEPSC, miniature EPSC; mIPSC, miniature inhibitory postsynaptic currents; PWT, paw withdrawal threshold; LVA, low-voltage activated; MIA, monosodium iodoacetate; SAP, saporin; SP, substance P; LC, locus coereleus; GLT-1, glutamate transporter; SNI, spared nerve injury; CPP, conditioned place preference; NAc DA, nucleus accumbens dopamine; rACC, rostral anterior cingulate cortex; β-FNA, β-funaltrexamine; EAAT3, excitatory amino acid transporters; PKC, protein kinase C; PMA, phorbol-12-myristate-13-acetate; PI3K, phosphatidylinositol-3-kinase

Source	Experiment	Result
Effect on dorsal root ganglion		
Biggs and colleagues[30]	Effect of gabapentin (100 μM) or pregabalin 10 μM for 5–6 days or 20 μM Mn^{2+} in suppression of HVA calcium currents in DRG neurons and spontaneous EPSCs at synapses in substantia gelatinosa	Strong effects were seen in medium-sized and in small DRG neurons, whereas large neurons and small neurons that bound isolectin were not affected
	DRG neurons: pregabalin (n=10–22), gabapentin (n=13–14), Mn^{2+} (n=5), control (n=6–13)	Mn^{2+} > gabapentin or pregabalin at ↓ HVA calcium currents in DRG neurons but not at suppressing EPSCs in substantia gelatinosa
	Substantia gelatinosa: pregabalin (n=6–14), control (n=8–10), Mn^{2+} (n=5)	
Yang and colleagues[25]	Chronically compressed DRG rats	TTX ↓ average number of spikes and abolished the spontaneous membrane potential oscillations
	Effect of gabapentin (5 μM; n=46) and TTX 100 nM (n=29) on firing, oscillations and resonance of DRG neurons; effect on persistent sodium current with bath application of gabapentin (1–20 μM; n=105)	Gabapentin ↓ resonant behaviour like TTX but in addition shifted peak resonant frequency indicating involvement of currents other than TTX-sensitive sodium currents. Gabapentin inhibited persistent sodium current with maximal inhibition at concentration of 20 μM
Effect on forward trafficking and recycling		
Bauer and colleagues[32]	SNL rat model- distribution of α2δ-1 in DRGs, axons and spinal cord in the ligated L5/L6 region compared with the non-ligated L4 region, effect of chronic pregabalin treatment on α2δ-1 distribution	↑ α2δ-1 expression on ipsilateral side after SNL but none on contralateral side based on immunofluorescence
		↓ α2δ-1 mRNA concentration in dorsal horn tissue than contralateral DRGs indicating that spinal cord neurons are not the source of increased of protein in the dorsal horn
	Two groups randomly assigned- SNL + pregabalin 30 mg kg^{-1} or SNL + saline, three daily injections until Day 9	↑ α2δ-1 at presynaptic nerve terminals
	Paw withdrawal frequency to mechanical and cooling stimulation before and after SNL up to Day 9 and 1 h after pregabalin, quantitative PCR and immunoblotting, immunohistochemistry including immunofluorescence, immunoelectron microscopy	Chronic pregabalin ↓ ipsilateral α2δ-1 immunofluorescence increases in dorsal horn and fasciculus gracilis but ↑mRNA in DRG was not affected. ↓ Paw withdrawal frequency. Proximal accumulation of α2δ-1 at the ligation site demonstrates anterograde trafficking
	Dorsal horn fluorescence intensity (L5, n=4; L4, n=11), paw withdrawal frequency: SNL + saline (n=12) or SNL + pregabalin (n=11)	
	α2δ-1 mRNA upregulation: SNL (sham, n=5; Day 7, n=4; Day 14, n=7); SNL + sallne (n=4); SNL + pregabalin (n=4)	
Tran-Van-Minh and colleagues[33]	Effect of gabapentin on the internalisation of, and insertion into the plasma membrane of α2δ-2 using an α-BBS-tagged α2δ-2 subunit, and a fluorescent derivative of α-bungarotoxin	↓ Cell surface fluorescence indicating reduced α2δ-2 concentrations at plasma membranes
		Internalisation rate was not affected
		Forward trafficking after exit from Golgi apparatus was affected
	Coexpression of Rab11 S25N, a dominant-negative mutant of Rab11 deficient in GTP binding to investigate recycling; effect of gabapentin on the trafficking of α2δ-2 through the fast recycling pathway dependent on Rab4-associated endosomes tested by coexpression of either Rab4 or the dominant-negative GDP-bound Rab4 S22N mutant with BBS tagged calcium channels	No effect of gabapentin on plasma membrane concentrations of α2δ-2 BBS with Rab11 S25N and calcium current
		Chronic gabapentin ↓ cell surface concentration of α2δ-2 BBS in the presence of either Rab4 or Rab4 S22N, suggesting that the effects are a result of prevention of α2δ-2 recycling from Rab11-positive recycling endosomes to plasma membrane
	Three independent experiments, number of cells per point time and condition- plasma membrane expression (20–42), internalisation (16–36), forward trafficking (14–41), Rab-11 recycling (23–65)	

Continued

Table 1 Continued

Source	Experiment	Result
	Chronic incubation with 100 μM or 1 mM gabapentin for 48 h before assessment of the plasma membrane expression level of α2δ-2 BBS	
Effect at neurotransmitter release sites		
Hoppa and colleagues[37]	Hippocampal neurons Effect of α2δ concentrations on the probability that a vesicle in the readily-releasable pool will undergo fusion with a single action potential stimulus and calcium influx ($n \geq 7$)	Single APs resulted in robust Ca^{2+} signals but ↓ by 40% in synapses overexpressing α2δ compared with controls. ↑ In action potential stimulus in spite of ↓ calcium influx suggests that overexpression of α2δ subunits results in a tighter spatial relationship between sites of Ca^{2+} entry and exocytosis
Matsuzawa and colleagues[38]	Effects of pregabalin 100 μM on excitatory synaptic transmission in superficial dorsal horn in syntaxin 1A knockout (n=12) and wild-type mice (n=11)	↓ Amplitude of electrically evoked eEPSC in wild type mice as compared to knockout mice
Zhou and Lou[39]	SNL model, α2δ1 overexpressing transgenic mice Effect of gabapentin (10–100 μg) on α2δ1 mediated presynaptic neurotransmission in superficial dorsal horn SNL model: mEPSC (SNL, n=58; sham, n=30); mIPSC (SNL, n=17; sham, n=17) Transgenic model: mEPSC (transgenic, n=20; wild type, n=22), mIPSC (transgenic, n=19; wild type, n=18)	↑ mEPSC frequency in superficial dorsal horn neurons after SNL and in transgenic mice normalised by gabapentin. No effect on amplitude. No effect on mIPSC in either model
Effect on thrombospondin		
Park and colleagues[42]	Gabapentin effect on intrathecal TSP4-induced neuropathic pain (n=8) or saline (n=6); effect on TSP4 mediated mEPSC frequency or control ($n \geq 7$ each) Intrathecal gabapentin (300 μg) effect on PWT in TSP4 induced neuropathic pain Gabapentin (50 μg) effect on elevated mEPSC frequency	Blocking the effect of C_{av}α2δ1 with gabapentin reversed TSP4 mediated pain ↑ PWT to near the control levels with intrathecal gabapentin, reduced to the pretreatment level after 24 h Elevated mEPSC frequency ↓ to the control level, but its basal level in the control group was not affected significantly
Pan and colleagues[43]	Effect of gabapentin (25 μM) pretreatment on the effects of thrombospondin-4 (TSP4) on HVA and LVA voltage-gated calcium channels HVA I_{Ca} (vehicle, n=9; gabapentin, n=7; TSP4, n=7; gabapentin + TSP4, n=7) and LVA I_{Ca} (vehicle, n=8; gabapentin, n=7; TSP4, n=7; gabapentin + TSP4, n=7) Calcium transients: HVA (vehicle, n=68; gabapentin, n=46; TSP4, n=66; gabapentin + TSP4, n=34), LVA (vehicle, n=40: gabapentin, n=53; TSP4, n=53; gabapentin + TSP4, n=39)	TSP4-induced reduction of HVA I_{Ca} and elevation of LVA I_{Ca} were eliminated by gabapentin. It also blocked effects of TSP4 on the intracellular Ca^{2+} transient
Effects on descending serotonergic facilitation, descending inhibition and cortical mechanisms		
Rahman and colleagues[47]	Osteoarthritis induced by intra-articular injection of MIA into the knee joint; spinal ondansetron (n=8, sham=8) or pregabalin (n=9, sham=8) on evoked responses of dorsal horn neurones to electrical, mechanical and thermal stimuli; pregabalin alone or with ondansetron (n=7) Spinal ondansetron (10–100 μg/50 μl) or systemic pregabalin (0.3–10 mg kg^{-1}); pregabalin (10 mg kg^{-1}) in pretreated MIA rats	Ondansetron: ↓ evoked responses to innocuous stimuli in MIA only, ↓ response to noxious stimuli in both groups Pregabalin: ↓ responses to noxious stimuli in the MIA-treated group only; efficacy lost in the presence of ondansetron
Suzuki and colleagues[48]	SNL model; gabapentin (10, 30, 100 mg kg^{-1} s.c.) after SAP and SP-SAP to target neurokinin-1 expressing neurons that drive serotonergic facilitation Effect of ablation of neurokinin-1 neurons with SAP: hind paw withdrawal frequency to mechanical/cooling stimuli: SNL (SAP, n=17; SP-SAP, n=23) sham (SAP, n=13; SP-SAP, n=9) Effect of SAP on neuronal plasticity: SNL (SAP, n=50–57; SP-SAP, n=41–44) sham (SAP, n=24–33; SP-SAP, n=21–32)	SP-SAP ↓ tactile and cold hypersensitivity and abnormal neuronal coding (including spontaneous activity, expansion of receptive field size) seen after SNL No neuronal response with gabapentin in absence of injury ↓ Punctuate, heat and brush evoked neuronal responses with gabapentin in SAP but not SP-SAP even in SNL Gabapentin effect lost with ondansetron pre-treatment; spinal 5HT3 activation allowed

Continued

Table 1 Continued

Source	Experiment	Result
	Effect of spinal 5HT3 block on gabapentin efficacy: intrathecal ondansetron 10 μg before gabapentin 100 mg kg^{-1}	gabapentin to inhibit responses in uninjured animals
	Spinal 5HT3 activation: spinal neurons of naïve, neuropathic SP-SAP, intrathecal activator 2-methyl 5HT 0.1 μg before gabapentin 100 mg kg^{-1}	
Suto and colleagues[50]	Effect on glutamate concentrations in LC with saline (normal, n=10; SNL, n=8) or gabapentin 50 mg kg^{-1} i.v. (normal, n=11; SNL, n=12)	↑ Glutamate concentrations in microdialysates from the LC compared with saline, with a peak effect of gabapentin 60 min after injection. ↑ Glutamate in both normal and SNL rats with local perfusion
	Gabapentin effect on increased glutamate after knockdown GLT-1 (n=22)	Knockdown of GLT-1 abolished gabapentin-induced increase in extracellular glutamate in the LC
	Depletion of noradrenaline with intra-LC injection of saporin 0.25 μg/rat (n=17)	Depletion of noradrenergic neurons did not alter gabapentin-induced increase in extracellular glutamate in the LC
	Effect on extracellular glutamate concentrations in spinal cord, vehicle or gabapentin 10 mM perfused into the spinal dorsal horn for 90 min (n=9 in each group)	In contrast to its effect in the LC, glutamate concentrations from the spinal cord reduced within 30 min compared with vehicle and was maintained for at least 90 min
Kimura and colleagues[51]	Effects of SNL on antihypersensitivity effects of gabapentin or saline (n=9 in each), single injection of intraperitoneal saline or gabapentin (100 mg kg^{-1}) at 0, 1, 2, 4, 6, 8, and 10 weeks after SNL surgery	For a large effect size (>30 g pressure) efficacy lost around 5 weeks; for middle (>20 g) and small (>10 g) effect sizes, efficacy lost at 6–10 weeks in half SNL rats
	Effects of intrathecal α2-adrenoceptor antagonist idazoxan (30 μg) or saline injected 30 min after gabapentin injection (100 mg kg^{-1}) in rats at 2, 6, and 10 weeks after SNL (n=7 or 8)	↓ Gabapentin efficacy at 2–6 weeks but not 10 weeks with intrathecal α2-adrenoceptor antagonist idazoxan -suggests that SNL time-dependently ↓ effect of gabapentin related to descending noradrenergic inhibition
	Effect of glutamate transporter GLT-1 selective small interfering RNA or control on effect on paw withdrawal with gabapentin 100 mg kg^{-1} (n=8)	↓ Expression of GLT-1 in LC at 6 weeks post SNL, ↓ gabapentin efficacy with GLT-1 small interfering RNA; Oral valproate treatment ↑ mechanical withdrawal thresholds compared with the control and restored the antihypersensitivity effect of gabapentin, which was abolished by idazoxan
	Effects of increasing GLT-1 expression in the LC by histone deacetylase inhibition on gabapentin's efficacy >6 weeks after nerve injury (n=9)	
	Sodium valproate (histone deacetylase inhibitor) by a feeding tube (200 mg kg^{-1} daily) for 14 days beginning 6 weeks after SNL surgery	
Lin and colleagues[52]	SNI model, brain glucose metabolic rate at the effective dose of gabapentin in SNI rats, (SNI, n=12; sham, n=10)	↓ Glucose metabolism in the media prefrontal cortex, anterior cingulate cortex, thalamus, and cerebellar vermis but ↑ in the bilateral upper lip regions of primary somatosensory cortex and ipsilateral AG
	18 F-fluorodeoxyglucose-positron emission tomography before and after SNI and after gabapentin	
Bannister and colleagues[53]	Effect of i.v. gabapentin 50 mg kg^{-1} on tactile allodynia (sham, n=7; SNL, n=9), CPP (sham, n=10; SNL, n=17), and NAc DA release (sham, n=11; SNL, n=12)	I.V. gabapentin ↓ allodynia with peak effect in 20 min, significant preference seen for the chamber paired with gabapentin- indicates gabapentin is not rewarding in a normal state, and that its rewarding quality in SNL rats is probably a result of relief of ongoing aversiveness associated with pain, ↑ DA only in SNL
	Effect of 200 μg intrathecal gabapentin on pain thresholds (saline, n=9; gabapentin, n=10), CPP (sham, n=10; SNL, n=12), NAc DA release (saline, n=7; gabapentin, n=8)	Intrathecal gabapentin ↓ pain thresholds, ↑ DA and preference for gabapentin chamber in SNL but not sham
	Effect of block with irreversible μ-opioid receptor antagonist β-FNA into the rACC in SNL on antiallodynia (saline, n=4; β-FNA, n=6) CPP (saline, n=7; β-FNA, n=12) and NAc DA release (saline, n=8; β-FNA, n=9)	Pretreatment with saline or β-FNA into the rACC did not influence gabapentin efficacy; robust CPP and ↑ DA with saline but no change in CPP or DA after β-FNA pretreatment—indicates endogenous opioid signalling in the rACC is required for rewarding actions but not antiallodynic effect
	Effect of gabapentin in rACC on allodynia (n=5 saline or gabapentin each), CPP (sham, n=10; SNL, n=8) or NAc DA concentrations (saline, n=8; gabapentin, n=5)	Gabapentin injected in rACC produced CPP, ↑ NAc DA release selectively in SNL rats but did not reverse tactile allodynia

Continued

Table 1 Continued

Source	Experiment	Result
Effect on glutamate transport		
Ryu and colleagues[58]	Voltage patch clamp of oocytes, effect of pregabalin on EAAT3 activity (n=20–25 in each group) and Michaelis constant (Km) and maximum velocity (Vmax) values of EAAT3 transport kinetics for glutamate (n=25 in each group) Effect of PKC activator (n=17–25 in each group: control, PMA, pregabalin, pregabalin + PMA) Effects of PKC inhibitors on EAAT3 activity (n=10–19 in each group: control, PKC inhibitor, pregabalin, PKC inhibitor + pregabalin) Role of PI3K on the regulation of EAAT3 activity by pregabalin (n=15–19 in each group)	Exposing oocytes injected with EAAT3 mRNA to serial concentration of pregabalin increased their responses to glutamate concentration dependently Pregabalin ↑ Vmax without changing the Km Treatment with PMA or pregabalin ↑ transporter currents but no additive effect PKC inhibitors ↓ pregabalin-enhanced EAAT3 activity, treatment with PI3K ↓basal EAAT3 activity Pregabalin ↑ EAAT3 activity and PKC and PI3K were found to contribute to this effect

membrane of neurons and glial cells.[58] However, gabapentin had an opposite effect with decreased EAAT3 activity in a similar model.[59] This discrepancy may be related to the duration of exposure to the drug. Oocytes were exposed to pregabalin for 72 h as opposed to 3 min to gabapentin.

Time course of action of gabapentinoids

The actions of gabapentinoids in neuropathic pain take several hours to develop *in vitro*, but develop rapidly *in vivo*.[31,60] A likely explanation is that the *in vitro* studies are often done in uninjured animals whereas the *in vivo* studies are done on nerve-injured animals where $\alpha_2\delta$-1 has been already upregulated.[31] The effects are probably pronounced with increased expression of $\alpha_2\delta$-1 subunit with a higher rate of turnover of channel complexes that may be more vulnerable to gabapentinoids.[31] The rapid effects *in vivo* may be a result of rapid intracellular neuronal uptake that is absent *in vitro*. Substantia gelatinosa neurons obtained *ex vivo* after acute administration of intraperitoneal gabapentin *in vivo* in chronic constriction injury model were less excitable.[61] The rapid effects may be a result of effects on descending serotonergic and noradrenergic pathways and cortical mechanisms that might be unrelated to increased $\alpha_2\delta$-1 expression). Selected studies relating to analgesic mechanisms are described in Table 1 and Fig. 2 illustrates a summary of these mechanisms.

Effect on inflammation and postoperative pain models

Elevated proinflammatory cytokines are intimately associated with the development of neuropathic pain as part of the neuroinflammatory response and are inhibited by gabapentinoids.[62–66] Neuropathic and inflammatory pain differ in their aetiology but have common underlying mechanisms such as elevated tumour necrosis factor, Nav1.7, Nav1.8, glutamate, increased glial activation, and glutamate receptor function.[67] Animal studies of inflammatory pain induce inflammation after injection of a wide range of irritants and evaluate reflexive behavioural responses to thermal, mechanical, or electrical stimuli. Gabapentinoids are effective antinociceptives in most animal models of inflammatory pain (Table 2).[68–83] However, some studies show limited effects.[84–87] Gabapentinoids reduce inflammatory mediators[69,73,78] and suppress dorsal horn activity[79,83] but contrasting effects have been shown.[84] There is some evidence to support pre-emptive treatment.[72,73,85] Gabapentin was effective in suppressing single motor unit response but not wind-up, indicating a peripheral mechanism of action.[86] Mechanical and thermal responses were attenuated but reduction in activity was not improved acutely as compared with non-steroidal anti-inflammatory drugs (NSAIDs).[87] Only chronic gabapentin had an effect on ambulatory-evoked pain.[76]

The neurophysiology of incisional pain, however, is different from inflammatory and neuropathic pain with unique sensitisation processes.[88,89] In the plantar incision model, a 1 cm longitudinal incision is performed through the glabrous skin, fascia, and plantar muscle of the rat hind paw. Short-lasting non-evoked guarding and longer lasting evoked pain-related behaviour are seen and used as surrogates for pain at rest and evoked pain (lasting several days to weeks) after surgery, respectively. Mechanical and heat but not cold hyperalgesia and anxiety behaviours develop after injury. The skin and muscle retraction injury model was developed to investigate prolonged pain after surgical incision. Gabapentinoids are effective in most animal models of postoperative pain (Table 2). They demonstrate analgesic effects with synergistic effects in combination with opioids and NSAIDs.[90–97] They did not influence activity in a knee arthroplasty model but improved weight bearing when combined with opioids in an incision model.[92,98]

Effects in human experimental pain models

Various models that explore the effect of gabapentinoids in human experimental pain have been described (Table 3). The Ultraviolet B (UVB) model is widely used for assessing efficacy of anti-inflammatory drugs.[115] Hyperalgesia is evoked by exposing an area of skin to an individualised dose of UVB. Gabapentinoids did not have any effect on heat pain perception and secondary hyperalgesia in this model of inflammation.[99,100] The burn model is considered a model of inflammatory pain but both central and peripheral mechanisms are involved.[116] Gabapentin did not have any effect on heat pain detection threshold, pain during burn and secondary hyperalgesia.[101] However, it reduced area of secondary hyperalgesia after brief thermal stimulation of thigh.[102] The capsaicin model is used as a surrogate model of changes in neuropathic pain resulting in sensitisation.[117] Gabapentin had limited effects on measures of hyperalgesia in this model.[103–105] Capsaicin mediates hyperalgesia through effects on

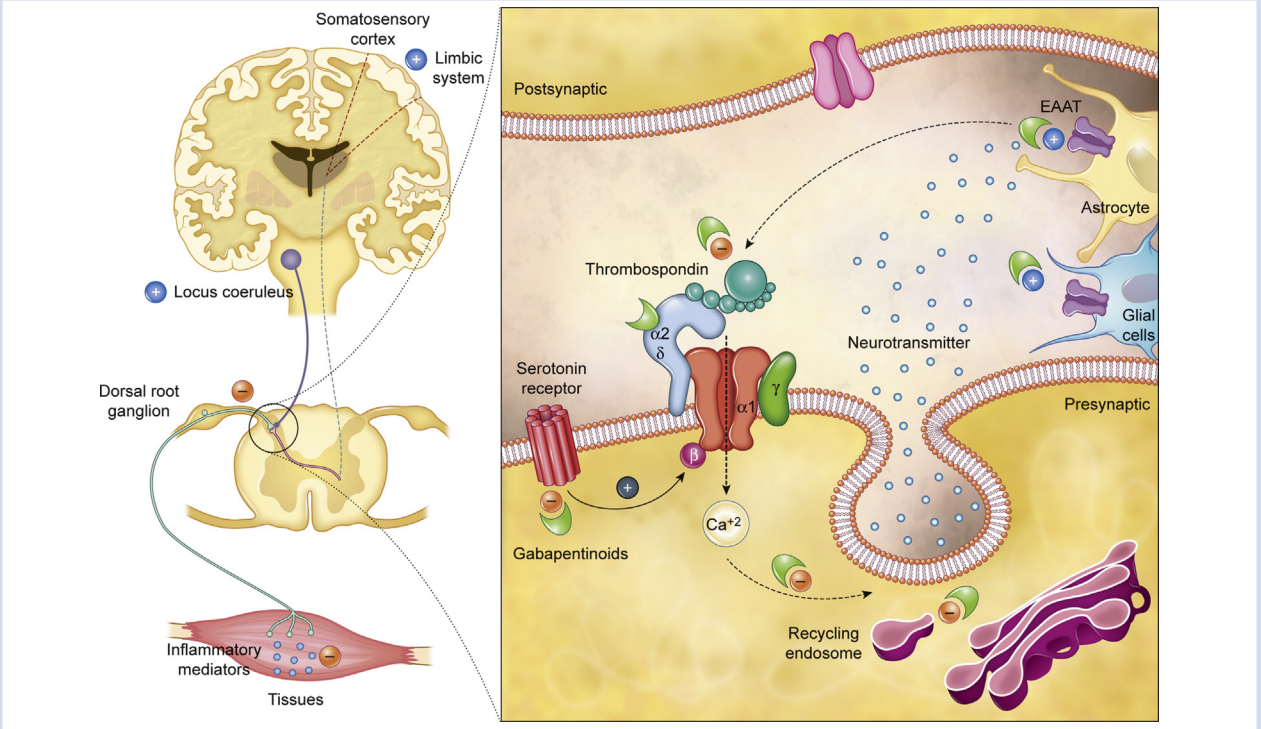

Fig 2. Gabapentinoids inhibit calcium mediated neurotransmitter release through effects on α2δ-1 subunits. They inhibit forward trafficking of α2δ-1 from the dorsal root ganglion, their recycling from endosomal compartments, thrombospondin mediated processes and stimulate glutamate uptake by excitatory amino acid transporters (EAAT). Mechanisms not directly related to neurotransmitter release at dorsal horn include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions and influence on the affective component of pain.

Table 2 Effects of gabapentinoids in animal pain models. CFA, complete Freund's adjuvant; FGF, fibroblast growth factor; PWT, paw withdrawal threshold; TNF, tumour necrosis factor; IL, interleukin; PKC, protein kinase C; ERK, extracellular signal regulated kinase; PWL, paw withdrawal latency; EPSC, excitatory postsynaptic currents; NS, nociceptive specific

Source	Experimental model	Result
Animal models of inflammation		
Sun and colleagues[68]	CFA induced arthritis (n=30 divided into control, treated and untreated group) Intraperitoneal gabapentin 50 mg kg^{-1} daily for 8 days starting 7 days after induction, FGF antagonist FD173074 2 mg kg^{-1} i.v. every 2 days	↓ Expression of FGF2 and FGF receptor 1 in dorsal root ganglia with gabapentin but ↑ in control ↑ PWT with gabapentin but ↓in control
Anfuso and colleagues[69]	Lipopolysaccharide stimulated rabbit corneal cells, endotoxin-induced uveitis in rabbits Gabapentin (10 μg ml^{-1}) or control, inflammation induced with lipopolysaccharide (1 μg ml^{-1}) for 24 h	↓ Expression of inflammatory mediators (TNF-α, IL-1β, phosphorylated protein expression, PGE2 and COX-2 in stimulated rabbit corneal cells), ↓ clinical signs and biomarkers of inflammation with topical treatment, at 7 and 24 h
Park and colleagues[70]	Glucose-6-phosphate isomerase (n=43) and collagen type II antibody (n=16) induced arthritis models with controls (n=4) Intraperitoneal gabapentin (100 mg kg^{-1}) or ketorolac (15 mg kg^{-1}) using a conditioned place preference paradigm	Collagen type II antibody model-gabapentin produced a preference in the early phase and a trend in the late phase, ketorolac ineffective Glucose-6-phosphate isomerase model-both gabapentin and ketorolac produced a preference for the drug-paired compartment in the early phase. Gabapentin, but not ketorolac, resulted in a place preference during late phase

Continued

Table 2 Continued

Source	Experimental model	Result
Zhang and colleagues[71]	Visceral inflammatory pain model (formalin induced colitis), gabapentin 100 mg kg−1 30 min before intracolonic injection Behavioural effects (n=9 in six groups), electrophysiological recordings (n=6 in seven groups), PKC translocation and ERK1/2 phosphorylation (n=6 in six groups for each)	↓ Pain behaviour with gabapentin at 30 min, no difference at 60 min; ↓ pain behaviour with PKC and ERK inhibitors at 30 min ↓ Firing in wide dynamic range neurons with gabapentin in 90 min after injection, ↓ at 30 min with inhibitors ↓ Translocation of PKC and ERK 1/2 phosphorylation with gabapentin, no difference at 120 min
Hummig and colleagues[72]	Orofacial capsaicin and formalin tests for pretreatment. (n=8−10), Inflammatory irritant carrageenan into the upper lip (n=8−10), constriction of the infraorbital nerve (n=7−8), facial cancer model Pregabalin 10 and 30 mg kg^{-1} 1 h before, control group (saline + pregabalin vehicle) and vehicle of the group; morphine 2.5 mg kg^{-1} as positive control in formalin group	Facial grooming induced by capsaicin abolished by pretreatment. No response to first phase (first 3 min) of the formalin response, but ↓ second phase (12−30 min after injection) at both doses. ↓ Heat hyperalgesia induced by carrageenan in lip, nerve injury and facial cancer
Dias and colleagues[73]	Carrageenan induced paw oedema: six groups (n=5 each); control, intraperitoneal saline, indomethacin 10 mg kg^{-1}, 0.1, 0.5, 1 mg kg^{-1} gabapentin 1 h before carrageenan Paw oedema induced by dextran, serotonin, histamine, bradykinin, PGE2, 48/80 (n=5 each for control, intraperitoneal saline, indomethacin, gabapentin 1 mg kg^{-1}) Carrageenan induced peritonitis- pretreatment with gabapentin 1 mg kg^{-1}, indomethacin or saline 1 h before (n=5 each)	↓ Paw oedema with gabapentin and indomethacin pretreatment in carrageenan and dextran induced oedema over 4 h, ↓ leucocyte counts in peritonitis model, levels of myeloperoxidase activity in the plantar tissue, IL-1β and TNF-α concentrations in the peritoneal exudates, ↑ concentrations of glutathione and ↓ malondialdehyde into the peritoneal fluid
Yang and colleagues[74]	CFA induced monoarthritis in rats; sham, control, gabapentin groups (n=6 each) Intraperitoneal gabapentin 100 mg kg^{-1} once daily for 4 days with the first injection 60 min before intra-articular CFA Thermal hyperalgesia and spinal microglia sham, arthritis, gabapentin (n=6 each); α2δ-1 concentrations (naive n=5, arthritis n=4, gabapentin n=3); CXCL3 concentrations (naive n=5, arthritis n=4, gabapentin n=3)	↓ Activation of spinal microglia, spinal voltage-gated calcium channel α2δ-1 subunits by Day 4, CX3CL1 concentrations and thermal hyperalgesia from Day 2−6
Abdel-Salam and Sleem[75]	Carrageenan induced paw oedema, intraplantar capsaicin, intraperitoneal acetic acid, gastric lesions caused by indomethacin or ethanol in rats (n=6 in each group, 2−4 groups and control) Gabapentin (12.5, 25, 50,100, 200 mg kg^{-1})	12.5 mg kg^{-1} produced analgesia. 100 mg kg^{-1} produced maximal increase in hot plate latency of 68% 1 h after administration. ↑ Current threshold in tail electrical stimulation with 25, 50 or 100 mg kg^{-1}. ↓ duration of paw licking after intraplantar capsaicin. No antinociceptive action in a mouse acetic-acid induced writhing assay. ↓ Paw oedema. ↓ Indomethacin induced gastric mucosal lesions with 12.5−50 mg kg^{-1} but higher doses increased gastric acid secretion
Vonsy and colleagues[76]	Unilateral knee OA using monosodium iodoacetate in rats Twice daily morphine (3 mg kg^{-1} s.c.) or gabapentin (30 mg kg^{-1} s.c.) or vehicle administered for 5 days; von Frey 1, 6, 8 g acetone drop (four groups each), latency to fall, ambulatory-evoked pain score (two groups each); n=7 for each group	↓ Mechanical and thermal sensitivity and ambulatory-evoked pain after both acute and chronic morphine whilst only chronic gabapentin had an effect
Zhang and colleagues[77]	CFA induced monoarthritis in rats Intraperitoneal injection of dexmedetomidine (2.5, 5, 10, and 20 μg kg^{-1}) or gabapentin (25, 50, 100, and 200 mg kg^{-1}) Monoarthritis rats divided into 15 groups in blind randomised fashion: drugs alone or in combination or normal saline, behaviour testing 15−150 min after injection (n=6−10 each group)	Dose dependent ↑ in PWL with both agents. ↓ Thermal hyperalgesia for 60 min with dexmedetomidine + gabapentin
Fehrenbacher and colleagues[78]	CFA induced inflammation in rats. Inflammation induced neuropeptide release with pregabalin, gabapentin (n=7 each) and untreated (n=14); effect on protein kinase C (PKC) activator induced neuropeptide release (n=3 each for pregabalin, gabapentin, untreated, PKC activator) 10 μM gabapentin or pregabalin on inflammation induced	Release of immunoreactive peptides from non-inflamed animals was not altered by either drug. ↓enhanced release of peptides after inflammation with both drugs. ↓ Release of immunoreactive neuropeptides in

Continued

Table 2 Continued

Source	Experimental model	Result
	neuropeptide release; pretreatment with 10 or 100 μM pregabalin for assessing effect of PKC activator induced neuropeptide release	spinal tissues pre-treated with PKC activator
Liu and colleagues[79]	Whole-cell voltage-clamp recordings from substantia gelatinosa neurons from adult rat spinal cord slices in carrageenan induced inflammation Gabapentin (5–20 μM for 5 min) or control, effect on monosynaptic and polysynaptic EPSC in normal (n=6 and 3) and inflammation (n=10 and 5); effect on *N*-methyl-D-aspartate induced currents	↓ Dorsal root Aδ fibre evoked polysynaptic, but not monosynaptic EPSC by 25%. No reduction in evoked polysynaptic or monosynaptic EPSCs in normal rats. Gabapentin failed to block *N*-methyl-d-aspartate induced slow excitatory currents.
Hurley and colleagues[80]	Carrageenan induced inflammation in rats (n=up to 17) Vehicle, gabapentin (3.0–300.0 mg kg^{-1}), naproxen (0.1–30.0 mg kg^{-1}), pregabalin (3.0–30.0 mg kg^{-1}) or a mixture of gabapentin and naproxen (0.0001–300.0 mg kg^{-1} total dose) or pregabalin and naproxen (0.1–30.0 mg kg^{-1} total dose); 17 groups for drugs alone (8–17 each group); 12 groups gabapentin + naproxen (8–16 each group); nine groups pregabalin + naproxen (7–17 each group)	Gabapentin + naproxen and pregabalin + naproxen can interact synergistically or additively to reverse thermal hyperalgesia associated with peripheral inflammation.
Patel and colleagues[81]	CFA induced inflammation in rats, gabapentin s.c. 30, 100, 250 mg kg^{-1} or vehicle (n=6 in each group)	↑ PWT, 40% reversal of hyperalgesia with 250 mg kg^{-1}
Lu and colleagues[82]	Carrageenan and kaolin induced arthritis in rats Intrathecal gabapentin or control (n=6 each) 1.5 h before induction in pretreatment; three groups for post-treatment: control, gabapentin in cord, gabapentin s.c. (n=6 in each group)	Pretreatment: at 4 h PWL response to radiant heat and the posture not changed, ↓ secondary hyperalgesia to radiant heat, no effect on knee circumference Post-treatment: at 1.5 h PWL back to baseline with spinal gabapentin, improved secondary hyperalgesia and pain behaviour, no effect on knee circumference; s.c. gabapentin did not affect PWL and pain behaviour
Stanfa and colleagues[83]	Carrageenan induced inflammation in rats Single unit extracellular recordings, effect of gabapentin (10, 30 and 100 mg kg^{-1} s.c.) in normal (n=5–6) and after carrageenan (n=5)	Gabapentin ↑ C-fibre evoked response of the dorsal horn neurones, ↑ post-discharge, ↑ Aδ fibre response with 100 mg kg^{-1}, none to Aβ; opposite effects after carrageenan
Camara and colleagues[84]	Sciatic nerve constriction, carrageenan induced paw oedema in rats Spontaneous behaviour (n=at least 10), effect on TNF-α, and IL-1β and IL-10 (n=at least 5 in each group) Oral gabapentin 30, 60, and 120 mg kg^{-1}, 60 min before chronic constriction of the sciatic nerve (CCSN) and for 5 days postinjury, saline as control	↓ Heat-induced hyperalgesia on the 5th day with 60 and 120 mg kg^{-1}. ↑ Nerve MPO, TNF-α, and IL-1β concentrations with 60 mg kg^{-1}, ↓ anti-inflammatory cytokine IL-10 nerve concentrations with 120 mg kg^{-1} ↑ Carrageenan-induced paw oedema and peritoneal macrophage migration with 60 and 120 mg kg^{-1}
You and colleagues[85]	Intact and spinalised rats: repetitive electrical stimulation of single DRG 97 NS neurons in the deep dorsal horn area of the spinal cord from 79 intact and 18 spinalised rats Pregabalin 20, 40, 80 mg kg^{-1} i.v., untreated control, saline-early and late response, after-discharges and windup; 80 mg/kg comparing intact and spinalised animals s.c. bee venom induced inflammation- mechanical/heat stimulation after pregabalin 80 mg/kg: (untreated n=8, saline n=8, pre-treatment n=9, post-treatment n=9)	↓ C-fibre mediated spinal NS neurons' late responses but effects on nociception not observed until 30 min after administration. No inhibitory effect on A-δ fibre mediated early responses. Inhibitory effects absent in spinalised animals, suggesting mainly central effects involving supraspinal centres via descending inhibitory controls. Markedly ↓ s.c. bee venom elicited spontaneous neuronal responses with pre-treatment but not post-treatment with pregabalin (80 mg kg^{-1}), and noxious mechanical/heat stimuli evoked hyperactivities of spinal NS neurons, suggesting role for pre-emptive analgesia
Curros-Criado and Herrero[86]	Carrageenan induced monoarthritis (n=6), sciatic nerve ligation mononeuorpathy (n=9), normal (n=6) Gabapentin 7–224 mg kg^{-1}, effect on single motor unit response to noxious mechanical stimulation	Gabapentin effective in arthritic and neuropathic rats but not normal rats; windup was dose dependently reduced in neuropathic but not normal and arthritic rats

Continued

Table 2 Continued

Source	Experimental model	Result
Matson and colleagues[87]	Bilateral inflammation of the knee joints by CFA in rats Multiple doses of ibuprofen, rofecoxib, celecoxib, piroxicam, and dexamethasone and gabapentin 300 mg kg^{-1}, amitriptyline 30 mg kg^{-1}; gabapentin and amitriptyline (five groups including control n=8 per group)	Reduction in activity was dose-dependently reversed by ibuprofen, rofecoxib, celecoxib, piroxicam, and dexamethasone, whereas gabapentin (3 h pretreatment) and amitriptyline were ineffective
Animal models of postoperative pain		
Papathanasiou and colleagues[90]	Rat plantar incision Morphine (1, 3 and 7 mg kg^{-1}), gabapentin (10, 30 and 100 mg kg^{-1}) or their combination (nine combinations in total)	Dose dependent synergistic effects with morphine + gabapentin
Narai and colleagues[91]	Rat plantar incision Intrathecal gabapentin (4, 40, 400 μg), two combinations with diclofenac or saline (n=6 in each group); 30 min before incision	Only 400 μg gabapentin ↑ PWT from 2 h up to 7 days. Gabapentin + diclofenac more effective than individual drugs
McKeon and colleagues[92]	Rat plantar incision Intraperitoneal tramadol 10 mg kg^{-1} + s.c. gabapentin 80 mg kg^{-1}, and saline, 30 min before incision (n=6 per group); tramadol repeated every 12 h for 60 h and gabapentin every 24 h for 48 h; tests after 1 day	Saline or tramadol group: hyperalgesia on Days 1–4 and 1–3 after surgery, respectively. Tramadol + gabapentin-reduced thermal hyperalgesia on Days 2 and 4. Only the combination did not show reduction in weight bearing
Flatters[93]	Skin/muscle incision and retraction in rats Intraperitoneal gabapentin 100 mg kg^{-1} or saline (n=9 each), testing after 9–13 days	100 mg kg^{-1} almost completely reversed mechanical hypersensitivity after 1 h
Hayashida and colleagues[94]	Rat plantar incision Oral (vehicle, 30, 100, 300 mg kg^{-1}) or intracerebroventricular gabapentin (vehicle, 10, 30, 100 μg; n=6 or 7 in each group), tests after 24 h; cerebrospinal fluid norepinephrine after preoperative gabapentin 1200 mg	↑ PWT for 1–4 h with oral and 15–60 min with intraventricular, effects reversed with α2-adrenergic receptor antagonist idazoxan and G protein-coupled inwardly rectifying potassium channel antagonist tertiapin-Q, ↑ norepinephrine concentration in cerebrospinal fluid
Whiteside and colleagues[95]	Rat plantar incision Intraperitoneal gabapentin (10, 30, 300 mg kg^{-1}) compared with different doses of morphine, celecoxib, indomethacin, etoricoxib, naproxen (n=8–10 each group)	↑ Pressure PWT, maximum reversal of mechanical hyperalgesia 64% with100 mg kg^{-1}, no effect at 5 h; maximum reversal of tactile allodynia by 19% as measured by von Frey withdrawal threshold, no effect at 1 and 5 h
Cheng and colleagues[96]	Rat plantar incision Intrathecal gabapentin 10, 30, and 100 μg, control (n=6–12 in each group), 2 h after incision	↑ PWT in dose dependent fashion
Field and colleagues[97]	Rat plantar incision Gabapentin 3–30 mg kg^{-1} s.c., 1 h before incision, control (n=8–12 in each group)	330 mg kg^{-1} ↑ thermal PWL with 30 mg kg^{-1} effective for 24 h; ↑ PWT with 10 and 30 mg kg^{-1} lasting for 25 and 49 h
Buvanendran and colleagues[98]	Knee surgery model in rats Knee surgery/drug, knee surgery/vehicle, sham skin incision/vehicle (n=8 in each group), evaluated after 24 h	Pregabalin 15 μg did not improve spontaneous activity postsurgery

transient receptor potential channel subfamily V member 1 (TRPV1). The heat-capsaicin model combines heat exposure with capsaicin to potentiate the effects, as TRPV1 receptors are also activated by heat. Gabapentin reduced secondary hyperalgesia and had modulatory effect on functional magnetic resonance imaging brain responses to nociceptive inputs in this model.[102,106] The electrical hyperalgesia model is considered representative of central sensitisation as repetitive electrical stimulation of skin and muscles can induce temporal summation. Contrasting effects were seen on the threshold of pain summation to this repetitive stimulation.[99,107] Area of allodynia was reduced.[108,109] Contrasting effects were also seen after sural nerve stimulation.[108,110] The continuous electrical stimulation model induces both central sensitisation and continuous C-fibre mediated pain. Gabapentin increased the current strength required to induce pain and reduced area of secondary hyperalgesia but did not influence pain detection threshold in area of hyperalgesia.[111] Gabapentinoids had modest effects on the pain tolerance threshold to single electrical stimulus.[99,111] Chemical stimulation of muscle by i.m. injection of hypertonic saline mimics musculoskeletal pain resulting in deep and diffuse pain as a result of activation of C-fibres.[117] Contrasting effects were seen with gabapentin.[107,111] Gabapentin reduced pain intensity in the cold pressor test model but only in combination with morphine unlike pregabalin that was effective alone.[99,112] Conditioned pain modulation, which is a measure of endogenous pain inhibitory pathways, was not influenced.[99,113] Pregabalin enhanced both opioid analgesia and respiratory depression.[114]

Discussion

Gabapentinoids certainly act on α2δ receptors and attenuate the enhanced dorsal horn excitability. It is, however, evident that various effects not directly related to neurotransmitter release at pre-synaptic terminals also contribute to analgesia.

Table 3 Effect of gabapentinoids in human pain models. UVB, ultraviolet B; CPM, conditioned pain modulation; PTT, pain tolerance threshold; PDT, pain detection threshold; MRI, magnetic resonance imaging; VAS, visual analogue scale

Source	Experimental model	Result
Okkerse and colleagues[99]	Battery of tests eliciting cutaneous electrical mechanical and thermal pain and included a UVB model, the thermal grill illusion, and a paradigm of CPM (n=16) Pregabalin 300 mg, pain measurements at baseline and up to 10 h post	↑ (PTT) for single electrical stimulus (10.8%), mechanical pain (14.1%), cold pressor (46.4%) and normal skin heat pain detection threshold (4.1%). No effect on single electrical PDT, no effect on repeat electrical PTT or PDT. No changes to thermal grill and CPM. No effect of pregabalin on PDT after UVB Dizziness (56%), somnolence (31%) and nausea (31%) with pregabalin.
Gustorff and colleagues[100]	Double-blind, active placebo-controlled, four-way cross-over design (n=16) Burn injury (UVB) model; gabapentin 600 mg, burn injury 20 h prior, comparison with remifentanil; PDT and PTT to heat in area of primary hyperalgesia and control, area of secondary hyperalgesia to pinprick	Gabapentin had no noticeable effect on heat PDT and PTT and the area of secondary hyperalgesia
Werner and colleagues[101]	Double-blind, randomised, placebo-controlled cross-over study (n=22) Burn injury model; gabapentin 1200 mg or placebo given on two separate days, burn injury after 3 h	↓ Mechanical allodynia in burn area but no significant reduction in heat pain threshold, pain during the burn, mechanical pain in area of secondary hyperalgesia, no effect in normal skin
Dirks and colleagues[102]	Double-blind, randomised, placebo-controlled cross-over study (n=25) Heat capsaicin sensitisation model, brief thermal sensitisation on thigh, long thermal stimulation; gabapentin 1200 mg; in primary hyperalgesia area PDT to heat; area of secondary hyperalgesia to pinprick and allodynia to brushing	↓ Secondary hyperalgesia in established heat capsaicin and brief thermal sensitisation. ↑ Heat PDT after long thermal stimulation but not in normal skin Light headedness more common with gabapentin but other side effects not different from placebo
Gottrup and colleagues[103]	Double-blind, randomised, placebo-controlled, parallel-group study (n=41) Capsaicin sensitisation model; gabapentin 300 mg increased to 800 mg three times per day (Days 10–15), measurements within 90 min after capsaicin on Day 1 and 15; intensity of spontaneous and evoked pain with pinprick and brush, area of hyperalgesia to pinprick and allodynia to brush, temporal summation of pain evoked by repetitive stimulation	No effect on spontaneous and evoked pain intensity ↓ Brush allodynia but no effect on area of pinprick hyperalgesia Fatigue, dizziness and headache more common with gabapentin
Wallace and Schulteis[104]	Double-blind, randomised cross-over study (n=13, three dropped out because of side effects) Gabapentin increased from 300 mg twice daily to 600 mg three times per day from Day 7–10, thermal and mechanical stimuli at 0, 4, 7, and 10 days, capsaicin on Day 10	No effect on acute sensory thresholds, pain, secondary hyperalgesia, or flare response induced by intradermal capsaicin. ↑ Side effects with gabapentin with sedation and dizziness most common
Wang and colleagues[105]	Double-blind, randomised placebo-controlled, four-period, cross-over study (n=20) Capsaicin model; pregabalin 300 mg, morphine 10 mg i.v., active placebo, placebo	Compared with active placebo pregabalin and morphine significantly ↓ area of secondary hyperalgesia over 15–240 min but not when compared with true placebo
Iannetti and colleagues[106]	Double-blind, placebo controlled, four-way cross-over with two paired randomised periods (n=12) Heat–capsaicin sensitisation model; gabapentin 1800 mg; MRI after 3 h, testing 45 min after capsaicin (before MRI) and at end of MRI	↓ Activations in the bilateral operculoinsular cortex, independently of the presence of central sensitisation ↓ Activation in the brainstem and stimulus-induced deactivations only during central sensitisation. The effect on deactivation was greater than on brain activation
Arendt-Nielsen and colleagues[107]	Double-blind, placebo-controlled (n=20) Single and repeated cutaneous and i.m. electrical stimulation; gabapentin 1200 mg; pain thresholds, stimulus-response function relating pain intensity scores to increasing current intensities for electrical skin and muscle stimuli, pain intensity (VAS) and pain areas after i.m. injection of hypertonic saline. Pain assessments were performed before, and at 4, 6, and 8 h after medication	↑ Temporal summation pain threshold in skin but not muscle, ↓ area under the pain intensity curve to hypertonic saline injections in the muscle and ↓ area of pain evoked by hypertonic saline
Boyle and colleagues[108]	Double-blind, placebo-controlled, three-period cross-over, four-treatment option, incomplete block study (n=30) Electrical hyperalgesia model; gabapentin 900 mg alone or with donepezil 5 mg for two of three periods, 50% randomised to placebo (negative control) or gabapentin 1800 mg (positive control) for the remaining period, each treatment period of 14 days; area of hyperalgesia to pin prick and touch evoked allodynia, single and repetitive electrical stimulation of sural nerve	↓ Area of allodynia with 1800 mg compared with placebo, ↓ area of hyperalgesia with combined gabapentin and donezepil compared with gabapentin alone. No difference in flare response. No difference in response to single or repetitive electrical stimulation of sural nerve Fatigue common with 1800 mg (43%)

Continued

Table 3 Continued

Source	Experimental model	Result
Chizh and colleagues[109]	Double-blind, two-period, placebo-controlled study using incomplete block design (n=32) Electrical hyperalgesia; pregabalin (titrated to 300 mg) or aprepitant (titrated to 320 mg), or placebo over 6 days, sensitisation was assessed over 3 h; at 2 h, either parecoxib (40 mg) or saline i.v.	↓ Areas of punctate mechanical hyperalgesia and dynamic touch allodynia with pregabalin, no response to aprepitant ↓ Area of allodynia with pregabalin + aprepitant but no effect on area of hyperalgesia
Enggard and colleagues[110]	Double-blind, randomised, placebo-controlled cross-over study (n=18) Pain summation model; gabapentin 600 mg three times per day over 24 h against placebo, sural nerve stimulation, tests before and 24 h after administration	↑ Threshold of pain summation to repetitive stimulation and PTT to single electrical sural nerve stimulation; no effect on PDT to single electrical sural nerve stimulation and cold pressor test
Segerdahl[111]	Double-blind, placebo controlled, three-session cross-over study (n=16) Hypertonic saline induced muscle pain, electrical stimulation; gabapentin 0, 1200, 1800 and 2600 mg (pre-treatment, titrated over four doses) or placebo; VAS, area of local and referred pain, PDT to pinprick in area of hyperalgesia	↓ Sensitivity to electrical induction of skin pain by 14% by pre-treatment with 1800 mg, ↓ area of secondary hyperalgesia but mechanical pain thresholds were unaffected. No effect on ongoing pain. Pain induced by i.m. infusion of hypertonic saline was not affected by gabapentin Dizziness and fatigue more common with increasing doses
Eckhardt and colleagues[112]	Double-blind, randomised, placebo-controlled four-way cross-over design (n=12) Cold pressor test; oral morphine 60 mg slow release or gabapentin 600 mg	Area under curve of pain tolerance from 0–6 h for gabapentin similar to placebo. However, gabapentin enhanced the analgesic effects of morphine
Olesen and colleagues[113]	Placebo-controlled study (n=64) Painful chronic pancreatitis; pain thresholds to pressure and electric tetanic stimulation and CPM after pregabalin 150–300 mg twice daily for 3 weeks	Electrical pain detection ratio but not CPM was predictive for pregabalin effect
Myhre and colleagues[114]	Double-blind, randomised, placebo- controlled, cross-over study (n=12) Cold pressor test; Pregabalin 150 mg/placebo twice orally, Remifentanil/placebo at effect-site target-controlled infusion: 0.6, 1.2, and 2.4 ng/ml; VAS score, spirometry, colour–word interference and rapid information processing	Pregabalin + remifentanil had additive analgesic effects but adversely affected cognition, pregabalin potentiated remifentanil induced respiratory depression

The absence of effects in spinalised animals supports the role of supraspinal mechanisms.[85] Elevated concentration of CSF norepinephrine after preoperative gabapentin indicates that some effects are mediated by descending noradrenergic inhibition.[94] However, there was no effect on conditioned pain modulation that is a measure of inhibitory influences.[99,113] The interaction of gabapentinoids with serotonin pathways is complex with permissive conditions for their effects dependent on the up-regulation of serotonergic facilitatory systems.[47,48] The role of serotonin in pain has not been fully elucidated with both facilitatory and inhibitory influences on nociception depending on the presence of injury.[118] This may explain the state dependent actions of gabapentinoids that have effects only in the presence of injury.[86,101] The influence on affective component of pain is independent of analgesic effects.[53] Pregabalin has well known anxiolytic effects that may have positive effects on postoperative rehabilitation.[119,120] The discrepancy between the acute effects *in vivo* as opposed to the prolonged duration of exposure required *in vitro* can be explained conceptually on the greater sensitivity of elevated levels of α2δ1 in nerve injury models to gabapentinoid action, rapid uptake by *in vivo* models, anti-inflammatory actions and by modulation of descending influences and the affective component of pain.

There are no studies looking at the role of α2δ in inflammation and incisional pain models. Elevated levels of α2δ-1 may be specific to neuropathic pain. Gabapentinoids seem to be effective antinociceptives in most animal models of inflammatory pain but prolonged administration may be required to achieve improved ambulation.[76] This explains the lack of improvement in activity in a model of complete Freund's adjuvant-induced arthritis.[87] Gabapentin was effective in all animal models of postoperative pain with synergistic effects with opioids. However, the difference in neurobiology of nociceptive systems between species limits the extrapolation of findings from animal studies to humans.[121,122] The few studies that have explored the effects in human models of inflammatory pain do not show convincing evidence of benefit.[99–101] It is difficult to explain the contrasting effects on pain induced by chemical stimulation of muscles and repetitive electrical stimulation. The lack of effect on secondary hyperalgesia induced by continuous electrical stimulation may be a result of the higher strength of current required in the premedicated group.[111] The lack of effect of gabapentin as compared with pregabalin in the cold pressor model may be a result of differences in pain assessment methods.[114]

There are no studies looking at effects in human models of postoperative pain. However, the effects on animal models suggest that gabapentinoids could contribute to multimodal analgesia. Several meta-analyses have shown a modest reduction in the use of opioids after surgery.[123–127] However, the quality of the trials is moderate to very low.[4] There is conflicting evidence with regards to the timing (preoperative or postoperative) and the optimal dose.[3] Although peak CSF concentrations are achieved at a median time of 8 h, the relevance is uncertain, as pregabalin in clinical doses does not influence spinal neurotransmitter concentrations.[29] The optimal dose has not been defined as the few studies that have attempted to

address this question, are limited by their sample size. Higher preoperative doses and continued use in the postoperative period may provide better analgesia.[3,128] This makes intuitive sense as $\alpha_2\delta$-1 concentrations are raised for several days after injury.[20] Only chronic use was associated with improved ambulation in a knee inflammation model.[76] This suggests that continued use is necessary for any potential benefit.

This approach might, however, increase the risk of adverse effects such as dizziness and increased sedation.[4] Gabapentinoids have synergistic analgesic effects with opioids but also enhance opioid-induced respiratory depression.[114] Significant number of healthy subjects in experimental studies experienced adverse effects, particularly with increasing dosage.[99,103,104,108,109] Gabapentinoids are often utilised in enhanced recovery pathways, particularly for hip and knee replacement surgery. These procedures are often performed in the elderly, who may be more vulnerable to the potential side effects of gabapentinoids.[129] It therefore makes intuitive sense to tailor the use of gabapentinoids to the clinical situation. Perioperative use is appropriate in patients having 'pro-nociceptive surgery', such as spine surgery that may be associated with nerve damage.[130] Patients on high dose opioids who are tolerant to their effects could benefit from even the modest effects of gabapentinoids. They might be helpful in situations where even marginal additional improvements in analgesia could potentially influence outcome (e.g. multiple rib fractures resulting in impaired ventilation as a result of poor pain control).[131]

The evidence for the role of gabapentinoids in prevention of chronic pain is limited. They have modest analgesic effects in chronic neuropathic pain with numbers needed to treat of 7.7 (6.5–9.4) for pregabalin and 7.2 (5.9–9.2) for gabapentin.[132] A Cochrane review suggested that gabapentinoids do not have a preventative role.[83] Recent systematic reviews have differing conclusions with regards to effectiveness in preventing persistent pain.[126,133] The lack of evidence may be because of inadequate sample size and poor trial designs.[134] It is not surprising, however, that a clear benefit in terms of prevention of chronic pain has not been found as, although $\alpha2\delta$-1 is required for rapid development of hypersensitivity, its absence does not prevent sensitisation.[17] This suggests that there are other mechanisms involved that contribute to the development of hypersensitivity. It is possible that these subunits are no longer upregulated in chronic pain, resulting in lack of efficacy.[135] The poor efficacy in chronic pain might be a result of differential upregulation of splice variants with reduced affinity to gabapentin.[136] Downregulation of glutamate transporter-1 can reduce long-term efficacy, but addition of valproate can restore efficacy.[51]

Translational studies studying the effects of analgesics in human models of postoperative pain are required to bridge the gap between human clinical studies and animal models. A human surrogate model of postoperative pain has been described.[137] There is no information regarding persistence of $\alpha2\delta$ upregulation in both animal and human studies. Future studies could focus on persistence of $\alpha2\delta$ and any possible correlation between the efficacy of gabapentinoids and concentrations of $\alpha2\delta$ and the presence of variants. This could allow targeted treatments with gabapentinoids for neuropathic pain and reduce the risk of exposing patients who might otherwise not benefit, to adverse effects. The potential of valproate to restore the efficacy of gabapentinoids needs to be explored. Well designed, large-scale trials are required to evaluate the effects on development of persistent pain.

Conclusion

The actions of gabapentinoids cannot be attributed solely to blockade of calcium channels. A more accurate description of their mechanism is depression of presynaptic excitatory input onto dorsal horn neurons through interactions with $\alpha2\delta$-1 subunits that are upregulated after injury. They inhibit forward trafficking of $\alpha2\delta$-1 from the dorsal root ganglion, their recycling from endosomal compartments, thrombospondin mediated processes and stimulate glutamate uptake by EAATs. Mechanisms not directly related to neurotransmitter release at dorsal horn include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions and influence on the affective component of pain. Gabapentinoids are effective analgesics in most animal models of inflammation and postoperative pain but effects in human models are variable. The risk of adverse effects is increased with increasing dosage. In situations where the risk–benefit balance is in favour of starting gabapentinoids, they should be started pre-emptively and continued throughout the perioperative period.

Authors' contributions

Conceptualisation, drafting, analysis and revisions of the manuscript: MC.

Declaration of interest

None declared.

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Appendix A

Search strategy

NICE Healthcare Databases search

Mechanisms of action

MEDLINE: 2214 records

((gabapentin).ti,ab OR exp PREGABALIN/ OR (Gabapentinoids).ti,ab) AND (exp 'GANGLIA, SPINAL'/ OR exp 'CALCIUM CHANNELS'/ OR exp 'SPINAL CORD DORSAL HORN'/ OR exp SEROTONIN/ OR exp 'GLUTAMIC ACID'/ OR (alpha 2-delta).ti,ab OR exp *BRAIN/ OR (thrombospondin).ti,ab)

EMBASE: 585 records

(exp GABAPENTIN/ OR exp PREGABALIN/ OR (gabapentinoids).ti,ab) AND (exp 'CALCIUM CHANNEL'/ OR exp 'SPINAL GANGLION'/ OR exp 'SPINAL CORD DORSAL HORN'/ OR exp SEROTONIN/ OR exp 'GLUTAMIC ACID'/ OR (alpha 2-delta).ti,ab OR exp *BRAIN/ OR (thrombospondin).ti,ab))

Additional records identified from other sources: 7

Records screened after duplicates removed: 2751; records excluded: 2654

Full text articles assessed: 97

Articles included: 41

Articles excluded: 56 (limited exploration of themes, repetition of theme)

Articles described: 16 (based on subjective evaluation of extent to which theme has been explored)

Inflammatory pain

MEDLINE: 373 results

(exp PREGABALIN/ OR (gabapentinoids).ti,ab OR (gabapentin).ti,ab) AND (inflamm*).ti,ab

EMBASE: 1136 results

(exp GABAPENTIN/ OR exp PREGABALIN/ OR (gabapentinoids).ti,ab) AND exp *INFLAMMATION/

Additional records identified from other sources: 4

Records screened after duplicates removed: 1482; records excluded: 1458

Full text articles assessed and included: 20

Postoperative pain models

MEDLINE: 428 results

'((gabapentin).ti,ab OR exp PREGABALIN/ OR (Gabapentinoids).ti,ab) AND exp 'PAIN, POSTOPERATIVE'/'

EMBASE: 1603 results

(exp GABAPENTIN/ OR exp PREGABALIN/ OR (gabapentinoids).ti,ab) AND exp 'POSTOPERATIVE PAIN'/

Additional records identified from other sources: 1

Records screened after duplicates removed: 1980; records excluded: 1971

Full text articles assessed and included: 9

Human pain models

MEDLINE: 2058 results

((gabapentin).ti,ab OR exp PREGABALIN/ OR (Gabapentinoids).ti,ab) AND (exp PAIN/ OR (experimental OR exp 'DOUBLE-BLIND METHOD'/)) AND exp HUMANS/

EMBASE: 606 results

(exp GABAPENTIN/ OR exp PREGABALIN/ OR (gabapentinoids).ti,ab) AND (exp PAIN/ AND *HUMAN/)

Additional records identified from other sources: 5

Records screened after duplicates removed: 2541; records excluded: 2525

Full text articles assessed and included: 16

Handling editor: J.G. Hardman