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REVIEW ARTICLE

A2δ ligands gabapentin and pregabalin: future implications in daily clinical practice

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Abstract

Gabapentin (GP) and pregabalin (PB) are structurally related compounds and their predominant mechanism of action is the inhibition of calcium currents via high-voltage-activated channels containing the a2d-1 subunit. A2δ ligands are approved for the treatment of pain of diabetic neuropathy and post-herpetic neuralgia in adults and as adjunctive therapy of partial seizures in children. Recently, pregabalin has been approved for treatment of anxiety disorders in Europe. Besides their already approved indications both drugs are promising treatment options for a number of different serious and debilitating diseases, as fibromyalgia, neuropathic pain of spinal cord injury, hot flushes, and essential tremor. In the present review, the unique mechanism of action of the above drugs is critically analyzed and evidence for their future use is provided. Gabapentin and pregabalin can be treatment options for these disorders, however, a clear comparison between the two drugs can not be performed, since there is no direct comparison study. The most common side effects are dizziness and somnolence which are also the most frequent reasons for withdrawal. Recommendations for future studies should include assessment of ideal titration period for GP and PB to reduce incidence of somnolence and dizziness and increase tolerability, cost-effectiveness and dose-response analysis of PB and GP and direct comparison of the two drugs. Hippokratia 2010; 14 (2): 71-75

Keywords: α2δ ligands, gabapentin, lyrica, neurontin, pregabalin

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Gabapentin (GP) and pregabalin (PB) are structurally related compounds and they are derivatives of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Gabapentin (Neurontin®, Pfizer) was originally designed as a GABAmimetic agent freely crossing the blood–brain barrier. Initially, it was evaluated as an antispastic agent as attenuator of the polysynaptic spinal reflex in animal models of spasticity[1]. As an anticonvulsant, it was first introduced as an antiepileptic drug. Later on, randomized controlled trials (RCTs) indicated its efficacy for postherpetic neuralgia[2], diabetic neuropathy[3], migraine prophylaxis[4], cancer pain and other chronic pain conditions.

Pregabalin (Lyrica®, Pfizer) is considered a successor to GP in terms of its basic chemical structure and therapeutic profile. It is approved in US and Europe for the treatment of pain of diabetic neuropathy[5] and postherpetic neuralgia[6] in adults and as adjunctive therapy of partial seizures in children[7]. Recently, it has been approved for treatment of anxiety disorders in Europe[7].

Very recent evidence from RCTs and systematic reviews indicate that both drugs are promising treatment options for many other serious and debilitating diseases, like fibromyalgia and neuropathic pain in spinal cord injury. In this review the unique mechanism of action of PB and GP is analyzed and evidence for their future use as treatment options for a number of diseases is provided. Furthermore, their advantageous safety/tolerability profile for the above indications is discussed.

Mechanism of action

Many cellular effects have been suggested for GP and PB, like modest actions on the GABAergic system[8] and on voltage-gated potassium channels[9]. However, the predominant mechanism of action which explains their pharmacological profile is the inhibition of calcium currents via high-voltage-activated channels containing the a2d-1 subunit, leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability[10]. This unique mechanism is consistently observed at therapeutically relevant concentrations in preclinical and clinical studies of GP and PB[11].

Gabapentin's effects are believed to be mediated by release of excitatory aminoacids and neuropeptides modulating the calcium channels and GABA transmission[12]. It has also been proven in animal models, that GP is effective in reducing allodynia and hyperalgesia[13-15].

Pregabalin is also an alpha-2-delta ligand which is structurally related to GABA. Data from preclinical studies suggest that it inhibits calcium currents via high-voltage-activated channels containing the a2d-1 subunit and reduces neurotransmitter (noradrenaline, serotonin, dopamine and substance P) release in hyperexcited neurons leading to attenuation of postsynaptic excitability[10,11,16].

A2δ ligands in Fibromyalgia

Fibromyalgia (FBM) is a very common chronic pain disorder[17]. It is characterized by widespread musculosk-

eletal pain and tenderness over discrete tender points. It frequently leads to debilitating symptoms like fatigue, sleep disturbance, depression and anxiety[17,18]. Fibromyalgia's prevalence is up to 2% of the United States general population and it steadily increases with age[19]. It is the second most common disorder as a cause for visits to rheumatologists and is associated with quite substantial morbidity and disability[20].

Although FBM is a debilitating disease, current treatment options are limited and mostly symptom based. Antidepressants and cyclobenzaprine have demonstrated the strongest evidence for efficacy[21]. These treatments though, are effective only over a short period of time and are poorly tolerated with many serious side effects. Recently, PB was approved by the FDA for treatment of FBM at 300 and 450 mg/day taken in divided doses twice daily. A recent meta-analysis analysed the efficacy and safety/tolerability of GP and PB in the treatment of FBM[22].

This meta-analysis concluded that GP is significantly superior to placebo in the primary outcome (pain severity score) and most of the secondary outcomes for the treatment of FBM. Generally, GP is well tolerated with no difference in withdrawals due to side effects between GP and placebo group[22]. Pregabalin was also shown to be effective in the treatment of FBM. Pregabalin at a dosage of 450 mg/day has the best Number Needed to Treat and Number Needed to Harm ratio[22].

Moreover, both drugs are effective in sleep disturbances associated with FBM. Sleep disturbances, like slow-wave non-restorative sleep, were reported to contribute to FBM symptoms, like fatigue and chronic pain[23]. It has been suggested that poor sleep is a key symptom of FBM[24].

Lastly, since FBM is characteristically a chronic condition, durability of efficacy is a very important issue. A recent 6-month randomized controlled trial examining the durability of efficacy of PB in FBM reported durable effects on pain and sleep disturbances in FBM patients[25], whereas amitriptyline and cyclobenzaprine failed to demonstrate the same durability[26].

Overall, the above mentioned data support a crucial role of GP and PB in treating FBM patients.

Table 1: Key points for gabapentin and pregabalin derived from this review.

- PB at a dose of 450 mg/day seems to be the best dosage regimen for treating fibromyalgia
- GP (1800 mg/day) is effective in treating fibromyalgia
- GP (3600 mg/day)and PB (600 mg/day) are effective in treating neuropathic pain in spinal cord injury
- GP is effective in the treatment of natural or tamoxifen-induced menopausal hot flashes
- GP as monotherapy (1200 mg/day) should be considered as treatment of limb essential tremor
- Side effects are dose-depended
- Tolerability is highly correlated to escalation period with longer titration period leading to better tolerability

GP gabapentin, PB pregabalin

A2δ ligands in Neuropathic pain of spinal cord injury

Spinal cord injury (SCI) is a leading cause of neuropathic pain (NP). Neuropathic pain is pain initiated by a primary lesion in the nervous system[27]. Typically, NP is characterized by abnormal pain perception and consists of severe clinical symptoms like burning, stinging and electric shock-like in quality pain[28]. This type of pain is frustrating for patients and poorly responds to standard pharmacotherapy. In SCI patients, NP causes emotional and physical discomfort, hinders rehabilitation therapies and leads to depressive symptomatology[29]. Unfortunately, NP in SCI is refractory and current treatments, like ketamine, antidepressants, baclofen, are not effective and their use is often limited by significant side effects[30,31].

Evidence suggests that GP and PB are promising treatment options. A recent evidence based systematic review evaluated GP and PB efficacy and safety/tolerability in treating NP in SCI[32]. This systematic review clearly indicates the efficacy of both pregabalin and gabapentin in NP of SCI. Gabapentin at a dose of 3600 mg/day is highly efficacious with minimal side effects[32,33]. The same efficacy for almost all efficacy outcomes was demonstrated for PB at a dosage of 600 mg/day[32]. Although a clear comparison between GP and PB can not be performed, PB appears to be more efficacious. As far as safety and tolerability concerns, GP appears to be safer. However, compared to other treatment options for NP in SCI, like tricyclic antidepressants and opioids, both drugs have limited side effects.

All evidence suggests that GP and PB should be considered as first line treatment options for NP in SCI.

A2δ ligands in Hot Flushes

"Hot flushes" (HF) is a term describing a clustering of symptoms associated with menopause[34]. Hot flushes typically involve a rapid-onset reddening of the skin on the chest, neck and head and a perception of increased body heat, accompanied by palpitations, irritability, anxiety and perspiration[35]. These symptoms are also observed in women receiving antiestrogen therapy (mostly tamoxifen) for breast cancer[36]. Approximately 70% of postmenopausal women will experience HF[35].

Although HF have a significant prevalence and usually a long lasting duration (2.5 years) after menopause, current treatment options are not satisfactory. Estrogen replacement therapy, although effective, is associated with side effects like cardiovascular events and breast cancer, which limit the target group suitable for treatment[37]. Selective serotonin reuptake inhibitors have also been shown to be effective in the treatment of HF, but many patients view their use for HF symptoms with distrust[38,39].

A recent metaanalysis analysed the efficacy and safety/tolerability of GP in the treatment of HF[40]. Overall, this study included 7 trials with a total of 901 patients. Total daily dosages ranged from 900 to 2400 mg/day. Four of these trials[41-44] examined patients with history of breast cancer, whereas the rest enrolled postmenopausal women[45-47]. The meta-analysis concluded that GP was associated with a significant reduction (20-30%) in both, frequency of hot flashes and composite score (an indirect marker of hot flash severity). Dizziness/unsteadiness and fatigue/somnolence were the most frequently reported adverse events associated with GP and resulted in a higher dropout rate, although they were of mild severity. Overall, all these data clearly indicate that GP appears to be effective in the treatment of natural or tamoxifen-induced menopausal HF.

There is still no evidence for the use of PB in the treatment of HF. One study though examining PB in HF is registered and will be completed in January 2009[48].

A2δ ligands in Essential Tremor

Essential tremor (ET) is a common adult tremor disorder[49]. Its prevalence is estimated to range from 0.4% to 5% and it increases with age[49]. Although the common misconception that ET is a benign condition exists, ET can cause substantial psychological and physical disability[50]. Patients with ET experience increasing difficulties in everyday activities like writing, drinking, dressing, eating, speaking[50].

So far, ET is often refractory to conventional pharmacotherapy and its drug treatment remains unsatisfactory[51]. Two commonly used drugs are propranolol and primidone. Propranolol is the only approved drug by the Food and Drug Administration (FDA). However, it is estimated that 30-50% of ET patients will not respond to these two treatment modalities[52]. Moreover, their use is accompanied by severe and potentially threatening side effects like ataxia, reduced arterial pressure, tachycardia, bradycardia and exertional dyspnea.

Gabapentin is approved as adjunctive therapy for partial complex seizures. Data from 3 RCTs suggest a possible role for GP in treating essential tremor[53-55]. Two studies reported little or modest improvement when GP was used as adjunctive therapy in doses of 1800 and 3600 mg/day[54,55]. The third study suggested that GP as monotherapy (1200 mg/day) significantly reduced tremor[53]. The same study suggested that GP and propranolol demonstrated significant and comparable efficacy in reducing tremor in all tremor measures. In all studies side effects were mostly of mild severity and mostly included dizziness, somnolence and fatigue. An evidence-based medicine systematic review concluded that GP as monotherapy should be considered as treatment of limb ET, whereas the data regarding GP use as adjunct therapy are conflicting and sparse[56].

Regarding PB, one recent RCT evaluated its efficacy and tolerability in treating ET[57]. Twenty two ET patients received PB at a dosage of 600 mg/day. They were evaluated by accelerometry and Fahn–Tolosa–Marin (FTM) rating scale. Pregabalin treated patients demonstrated a significant reduction in tremor amplitude and significant improvement on tremor limb scores. Pregabalin was well tolerated.

This evidence suggests that GP and PB are promising treatment options for ET, but the need for more evidence exists. One RCT evaluating the use of PB in treating ET is currently registered in recruiting status and expected to be completed at December 2009[58]. Future RCTs should include a direct comparison of GP and PB with established treatments and larger sample sizes.

Safety/tolerability

Safety/tolerability is an issue of great importance when treating chronic diseases like FBM, NP in SCI and ET. Patients with such diseases have an already heavily affected health status. Gabapentin generally demonstrates very few side effects and non organ toxicity[3]. Pregabalin has great bioavailability profile. Its minimal interaction with other medication and lack of interference with hepatic enzymes are important advantages that contribute to its safety profile.

Specifically, the most common side effects of PB and GP are dizziness and somnolence[59,60]. These two symptoms are also the most frequent reasons for withdrawals. Generally, all side effects are of mild or moderate severity. Both drugs are well tolerated and have little side effects compared to other treatment options like tricyclic antidepressants, ketamine, opioids and non-steroidal anti-inflammatory drugs[61,62]. Opioids for example, although a well established treatment for chronic pain conditions, have side effects like analgesic tolerance, withdrawal reactions after discontinuation and possibility for addiction, which can not be ignored[63].

Of most importance is the fact that all studies indicate a dose-related incidence of side effects[32]. It is also suggested that titration period is a key factor in reducing incidence of somnolence and dizziness. Slower escalation periods decrease the incidence of dizziness and somnolence and lead to better tolerability[32]. Future trials should focus on this, in order to determine the best schema employed.

Discussion

This article reviewed new evidence regarding the use of PB and GP and provided new insights for future clinical implications. Unfortunately, a clear comparison between the two drugs can not be performed, since there is no study directly comparing them. Since PB is still expensive, cost-effectiveness studies should be performed. Recommendations for future studies should include assessment of ideal titration period for GP and PB to reduce incidence of somnolence and dizziness and increase tolerability, cost-effectiveness and dose-response analysis of PB and GP and direct comparison of the two drugs.

Conflict of interest

The authors state no conflict of interest

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