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Review Article

GABAPENTIN: A PHARMACOTHERAPEUTIC PANACEA

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ABSTRACT

Gabapentin (GBP) is a second generation anticonvulsant whose exact mode of action is not known. It was approved as adjunctive treatment in patients 12 years or older with partial seizures, with or devoid of secondary generalization. Soon after, it was approved by the German regulatory authorities for "Neuropathic pain in adults" particularly painful diabetic neuropathy and post herpetic neuralgia. Recently GBP has proved as an efficient multimodal perioperative drug in the field of anaesthesia. It is also effective in improving symptoms of Restless Leg Syndrome by reducing the frequency of periodic leg movements and improving sleep quality. GBP appears to be effective and well tolerated treatment modality for hot flashes in post menopausal women. Moreover, it is also being prescribed as a prophylactic treatment for migraine. In view of its multiple pharmacotherapeutic effects combined with its favorable side effect profile in various patient groups (including the elderly) and lack of drug interaction, makes it an attractive agent.

Keywords: Gabapentin, Anti-epileptic drugs, Neuropathic pain, Perioperative drug, Restless leg syndrome, Hot flashes, Migraine.

Chemistry

Gabapentin (GBP), [1-(aminomethyl)cyclohexane acetic acid], is a conformationally restricted analog of the neurotransmitter γ-aminobutyric (GABA), with a cyclohexane ring incorporated (Fig.1). It is neither metabolically converted to GABA or its antagonist, nor is it an inhibitor of GABA uptake or degradation.

It has a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.34. It is bitter tasting white crystalline substance, and is freely soluble in water in both basic and acidic aqueous solutions. At physiological pH, it is highly charged, existing as a zwitterion with a pKa1 of 3.68 and a pKa2 of 10.7 at 25°C [1]. It is assayed in both plasma and urine by gas chromatography [2] and high performance liquid chromatography [3]. As such, the structure is stable at room temperature, but in aqueous solutions, small amount of lactam formation can occur but this is minimized at a pH of 6.0 [4].

Pharmacokinetics

Naturally occurring amino acids (and also gabapentin) are dually ionized at neutral pH. Because of this phenomenon they are not very soluble in lipids and have very little permeability to cell membranes by diffusion. To facilitate the transport of various amino acids across the cell membranes, several families of specialized membrane-bound proteins have evolved [5].

GBP is available as oral preparation and is transported across the gut membranes into the blood stream by a saturable mechanism similar to the large, neutral amino acid carrier (system-L) of gut tissues [6]. Since it follows saturation kinetics, the oral bioavailability varies inversely with dose. After a single dose of 300 or 600mg bioavailability was found to be approximately 60% and 40% respectively [7,8] and this decreases to further 35% at a steady state with doses of 1600mg thrice daily. After ingestion of single dose of 300mg, peak plasma concentrations (Cmax) of 2.5–3 µg/ml are achieved 2 to 3 h (i.e., Tmax) [7, 10, 11]. Because of the saturable transport system and the non linear absorption of gabapentin, Cmax increases less than threefold when the dose is tripled from 300 to 900 mg [9].

The volume of distribution of GBP is approximately 0.6–0.8 L/kg [7, 9]. Concentrations of GBP in human cerebrospinal fluid (CSF) are 5-35% of plasma levels [12] and have been estimated at between 0.09 and 0.14 µg/ml [13]. GBP levels in human brain are 80% of those in serum, a finding conforming animal distribution studies [14].

In humans, GBP is not metabolized [15]. Neither isoenzymes nor genetic factors operating to give rise to metabolic differences among individuals are known or expected. In humans, no metabolites of GBP were found by any researcher so far [9, 16]. It is eliminated unchanged in the urine and any unabsorbed drug is excreted in the faeces [12]. It undergoes first-order kinetic elimination (elimination rate constant) and plasma clearance and renal clearance are linearly related to creatinine clearance. Therefore, renal impairment will consequently decrease GBP elimination in a linear fashion with a good correlation with creatinine clearance [9, 12, 15, 17]. Dose need to be adjusted in patients with impaired renal function. The elimination half-life of GBP is between 4.8 and 8.7 h [7, 10, 16 17-19]. GBP is removed by haemodialysis, so after each treatment, patients in renal failure should receive maintenance dose of GBP so as to provide steady state concentration of the drug [20].

Drug Interactions

GBP neither induces nor inhibits hepatic microsomal enzymes; neither does it affect the plasma concentration of the most concurrently administered AEDs [9]. Other AEDs have no effect on the GBP pharmacokinetics [21]. GBP shows low protein binding in hepatic cells and also lacks any sort of hepatic metabolism. Cimetidine, decreases the clearance of gabapentin by 12% by decreasing the glomerular filtration rate (GFR) [9]. Antacids reduce the bioavailability of GBP from 10% (when given 2 h before GBP dose) to 20% (when given concomitantly or 2 h after GBP) in healthy individuals [22].

Mechanism of Action

Despite its design as GABA analogue, neither GBP nor pregabalin mimics GABA when iontophoretically applied to the neurons in primary culture. Although GBP is well established as an effective anti-epileptic and anti-neuropathic pain drug, the underlying molecular mechanism of GBP is still not entirely clear [23]. GBP does not interact with any GABA subtype receptors [24, 25]. No concrete evidence is reported from any study that GBP binds substantially to any subtype of $GABA_B$ receptors [24, 26, 27].

One study is suggestive of agonistic action of GBP on a subset of $GABA_B$ receptors [28], which may negatively regulate voltage gated Ca^{2+} channels [29] and activate inwardly rectifying K^+ channels [30]. Additionally, GBP is able to block Ca^{2+} and Na^+ channels [31] and open K^+ channels [32]; thereby inhibiting the abnormal spontaneous activity and hyper-excitability of sensory neurons, thus ameliorating pain. Currently the most plausible mechanism for the action of GBP is that it may act at the $\alpha_2\delta$-1 subunit of voltage gated Ca^{2+} channels (VGCC) [33], as observed in pig cerebral cortex membranes [34].

Moreover, it has been speculated that anticonvulsant effect of GBP are mediated by $\alpha_2\delta$-1 subunit, but whether and how the binding of GBP to the $\alpha_2\delta$-1 regulates neuronal excitability remains unclear still. It is envisaged that after the binding with $\alpha_2\delta$-1 subunit it

decreases the neuronal excitability. The binding is also instrumental in inhibiting the calcium currents and in prevention of extracellular calcium entry, which is essential for subsequent vesicular exocytosis [35-37]. Evidences also show that GBP is an inhibitor of calcium channel subunit trafficking [38, 39]. Nevertheless, it is unclear whether the anticonvulsant and analgesic effects of GBP and pregabalin are mediated by effecting Ca^{2+} currents and if so, how? However, an increase in the VGCC $\alpha_2\delta$-1 subunit (an analgesic target of GBP) in the dorsal spinal cord has been reported in diabetic and paclitaxel induced pain [38, 40].

Adverse Drug Reactions

GBP is usually well tolerated drug; however, dose limiting side effects may prevent some patients from achieving therapeutic plasma levels. The therapeutic levels of GBP are 2-15µg/l. In a controlled clinical trial, conducted by Ramsay [41] it was reported that somnolence (20%), dizziness (18%), ataxia (13%) and fatigue (11%) were the most common side-effects (See Table 1).

In yet another, large open-label multicentre study involving 2216 patients to examine the safety and tolerability of GBP as an adjunctive therapy in seizure control, showed that the most common adverse effects were somnolence (15.2%), dizziness (10.9%) and asthenia (6.0%). The most serious adverse effect was convulsions (0.9%) [42].

Gastrointestinal discomforts are among the most common adverse effects of antiepileptic drug including GBP. The incidence of the occurrence of the diarrhea, dysphagia or heart burn was significantly increased when GBP was added to other AEDs as was studied by Jahromi et al., [43].

Teratogenesis

In a study conducted by Molgaard-Nielson et al., [44] the first trimester exposure to GBP compared with no exposure to the drug was not associated with an increased risk of major birth defects among live born infants in Denmark.

Therapeutic Indications of Gabapentin

Gabapentin: An Antiepileptic Drug

The epilepsies are the common and frequently devastating disorders, affecting approximately 2.5 million people in the United States alone [45]. GBP is one of the newest antiepileptic drugs, which was licensed for use in the United Kingdom and United States in as early as 1993 [46]. GBP has proved to be efficacious as an adjuvant to other anticonvulsant in the treatment of partial and secondary generalized tonic-clonic seizures in patients over 12 years of age [47].

Partial Epilepsy

In a meta-analysis of five placebo controlled clinical trials conducted by Leiderman [48], GBP was conformed as an effective drug in partial epilepsy using doses varying between 900mg to 1800mg per day. Some studies with class I evidence assessed the effectiveness of GBP in patients with intractable partial seizures [49]. In another study, patients with partial epilepsy were put on doses varying between 600mg to 1800mg per day [50]. In a prospective study conducted by Rajna P and Szijarto E [51] GBP was found efficient and safe in idiopathic or crypto/symptomatic partial epilepsy in adults. Marson et al. demonstrated its efficacy as an add-on therapy in patients with drug resistant partial epilepsy [52].

Three large multicentric, double blind, randomized dose controlled trials involving 649 patients demonstrated efficacy and safety of GBP as a monotherapy in partial seizures [53]. Study conducted by Herranz JL [54] concluded that GBP is an efficient drug and is well tolerated by children and adolescents with partial epilepsy, when employed in polytherapy or as monotherapy. Snacho-Rieger J and Lopez-Trigo J showed that GBP is an efficient, favourably tolerated drug utilized as monotherapy in partial epilepsy [55]. Delahoy et al. [56] conducted a randomized placebo controlled trails to compare the efficacy of pregablin and GBP at comparable effective dose levels in patients with refractory partial epilepsy and concluded that pregablin is likely to be more effective than GBP at comparable effective doses. These results were based on clinical response and the number of seizure free days (SFD) over the last 28 days. A double blind, placebo controlled trails of adults with refractory partial seizure demonstrated that addition of GBP or pregabalin to other anti-seizure drugs is superior to placebo [57, 58]. Another double blind study of GBP (with 900mg to 1800mg per day) monotherapy disclosed that GBP was equivalent to carbamazepine (600mg/day) for newly diagnosed or generalized epilepsy [59].

Psychotropic effects of GBP have also been studied [60, 61]. A double blind study of 210 patients with uncontrolled partial seizures was conducted who were converted from one to two anti-epileptic drugs to GBP monotherapy. Improvements were observed in emotional and inter personal adjustment after administration of GBP [61].

Geriatric Epilepsy

Epidemiological studies indicate that the occurrence of epilepsy increases significantly after 60 years [62]. Epileptic treatments in this age group is a matter of challenge because of the concomitant medical illness, polytherapy, decreased renal and hepatic function, alteration in pharmacokinetics (pKa) and changed CNS pharmacodynamics [63]. Because of the favourable side-effect profile and promising pharmacokinetics, GBP seems to be one of the choicest drugs in elderly [64, 41]. In a study conducted by Gil-Nagel et al., on the assessment of GBP in the treatment of epilepsy on elderly showed that GBP has advantageous pharmacokinetic characteristics such as lack of hepatic metabolism, no protein binding and easy to estimate regime for patients with renal failure in elderly [65].

Generalized-Onset tonic clonic Seizures

According to randomized controlled trails efficacy and effectiveness evidence, GBP is possibly efficacious as initial monotherapy for adults with generalized onset tonic clonic seizures [66-68]. Either no data or insufficient efficacy data is available to determine whether GBP could be prescribed for initial monotherapy for children with newly diagnosed or untreated generalized tonic clonic seizures [69].

Seizure in Stroke Patients

Stroke patients in adult and elderly age group have a predilection for epilepsy. GBP and lamotrigine have been approved to be more effective than carbamazepine in elderly patients with stroke because they don't interact with anticoagulant (warfarin) and anti-platelet agents that are prescribed in these patients [70]. GBP offers successful anti-epileptic treatment especially in specific patient populations with partial epilepsy in whom the pharmacokinetic and/or safety profile of GBP would make it a desirable alternative as monotherapy. These are the patients who suffer hepatic diseases, porphyrias, elderly patients on polytherapy and children with benign partial epilepsy of childhood.The safety of GBP and its lack of drug-drug interactions is also beneficial in patients with partial seizures who are getting simultaneous treatment with immunosuppressive drugs [71-74].

Gabapentin: Uses in pain management

Among the newer anti-epileptic drugs (AEDs) GBP expanded its use, shortly after it was labeled and marketed for partial seizures with or without secondary generalizations, into a broad range of neurologic and psychiatric indications [75].

On October 23, 2000 GBP was approved by the German regulatory authorities for "Neuropathic pain in adults" particularly painful diabetic peripheral neuropathy (PDN) and post herpetic neuralgia (PHN) [75].

Neuropathic pain

The International Association for the study of pain (IASP) defines neuropathic pain as "a type of chronic pain caused by a lesion or disease of the somato-sensory nervous system. Lesion means the direct damage to sensory nervous system, while disease refers to indirect injury by metabolic stress, autoimmune conditions or inflammatory and so on" [76]

The classification of the neuropathic pain can be presented on the basis of etiological factors. Major forms of clinical neuropathic pain are given in Table 2 [77].

It is estimated that neuropathic pain affects millions of people worldwide [78]. This pain reduces the patient's overall health related quality of life (Sleep, mood, work, social and recreational capacities) and general health care costs several times than in control group [79].

Neuropathic pain may be spontaneous in nature (continuous or paroxysmal) or evoked by sensory stimuli. The chief symptoms of Neuropathic Pain include spontaneous lancinating, shooting or burning pain; hyperalgesia and allodynia; or any combination of such pain [80].

It is possible for patients to present with pain in the context of sensory loss. Unlike inflammatory pain, Neuropathic Pain serves no biological advantage and can be described as an illness in its own right.

Typically, Neuropathic pain does not respond as well to conventional analgesics, such as paracetamol and NSAIDs. Many patients are resistant to current therapy, and thus there is a pressing need to further develop novel medications for the treatment of neuropathic pain [81].

Guidelines for the pharmacological management of Neuropathic Pain in non-specialist setting have been published (NIH, 2010) [82].

Gabapentin and Pregablin as First Line drugs for neuropathic pain

Among the pharmacotherapies currently used to treat Neuropathic pain conditions are the AEDs. Carbamazepine, GBP and pregabalin that are among the first line treatment options for several Neuropathic pain conditions [83-86]. GBP and pregabalin selectively bind to the $\alpha_2\delta$-1 subunit of calcium channels in various regions of brain and the superficial spinal dorsal horn. As a result, it inhibits the release of excitatory transmitters such as glutamate, nor-epinephrine and substance P [87].

Specific neuropathic pain syndromes

Diabetic peripheral polyneuropathy

Nerve damage and neuropathy is one of the long term complications of diabetes mellitus and is most prevalent in elderly patients with type II DM. The rising prevalence of type II diabetes is likely to increase the burden of diabetic peripheral neuropathic pain (DPNP) [88]. The main symptom of DPNP are burning or shooting pain in the lower limbs and feet, usually occurring for more than three months. At the moment the main aim of pharmacological treatment in DPNP is to control pain as there is no approved treatment to restore nerve function.

A double blind, placebo controlled, parallel group multi centric study of 165 diabetic patients with a 1-5 year history of DPNP reported a beneficial effect with GBP [89]. 84 patients were put on GBP and 81 on placebo. A statistically significant (P<0.0001) reduction in mean daily pain scores (using an 11 point Likert Scale) in the GBP group (baseline 6.4, end point 3.9); compared with placebo (baseline 6.5, end point 5.1), was achieved. The number of patients needed to be treated for one patient to receive at least 50% pain relief for the analgesic effects in neuropathic pain with GBP in this study was 3.8 [90]. Another double blind, placebo controlled trail of GBP in 32 diabetic patients with neuropathic pain showed a statistically significant analgesic effect during the first month of treatment [91].

A randomized, double blind cross over study was conducted by Morello et al. [92] in which efficacy of GBP was compared with amitryptyline in DPNP patients, which found both drugs ameliorated pain equally.

In another study done for a period of 12 weeks involving 25 randomised patients (13 received GBP, 12 received amitriptyline), GBP significantly reduced pain scores (p=0.026) and paraesthesia (p=0.004) compared with amitriptyline [93]. Adverse effects were also less frequent in GBP group (p=0.003).

Post herpetic neuralgia

Post herpetic neuralgia (PHN) is a neuropathic pain syndrome that results from an insult to the peripheral and CNS caused by varicella zoster virus (VZ virus). Nerve lesions caused directly by the virus or the inflammatory response can trigger molecular changes in nociceptive neurons leading to channelopathies contributing to the experience of pain [94-96]. Spontaneous pain may result in the persistent sensation of burning, tingling or aching and may be associated with thermally or mechanically provoked pain resulting in hyperalgesia or allodynia [97].

PHN is one of the commonest and most studied neuropathic pain conditions. It is most common in the ageing population because the majority of cases occur in patients over the age of 50 years; with the incidence doubling by the age of 80 years [98].

Of patients with herpes zoaster who are of ages ≥50 years, as many as 10%-20% will develop PHN [99]. PHN results from reactivation of the VZ virus contracted years beforehand, which typically produces a well-defined dermatological rash. PHN is typically defined as pain and/or dysesthesia at 12 weeks after resolution of the rash. The pharmacological treatments approved by FDA for the treatment of PHN are GBP, pregabalin and 5% lidocaine patch [100].

In January 2011, FDA approved Gralise as a once daily dose of GBP 1800mg for the treatment of PHN [101]. Gralise is a one daily extended release formulation of GBP developed by Depomed Inc (Menlopark, CA, USA), using AcuForm technology. AcuForm is a polymer based drug delivery system that retains the tablet in the stomach and upper GIT for a sustained period of time. When administered with a meal the tablet expands, is retained in the stomach, and gradually releases the drug over an approximately 10 hour period via a polymer matrix [102]. Rowbotham et al [102] conducted a multicenter, randomized, double blind, placebo-controlled, parallel design, 8 weak study involving 229 subjects with PHN, which demonstrated the efficiency of GBP in the treatment of PHN. The study showed a statistically significant (p<0.001) decrease in pain scores (using an 11 point likert scale) from 6.3 to 4.2 for the GBP group, compared with 6.5-6.0 in the placebo group.

Trigeminal neuralgia

Trigeminal neuralgia presents as abrupt, intense bursts of severe, lancinating pain, provoked by touching sensitive trigger areas on one side of the face. The disorder may spontaneously remit for periods of several weeks or months [77]. Traditional anticonvulsant (carbamazepine, phenytoin and lamotrigine) are used as the first line treatment. These are sometimes discontinued because of adverse effects. An open label trial [103] and case reports [104, 105] have shown the efficacy of GBP for trigeminal neuralgia. In an open label trial 13 patients with idiopathic trigeminal neuralgia were put on GBP between doses ranging from 600-2000 mg/day. The patients experienced a significant pain relief with GBP over a mean follow up period of 6 months as compared with carbamazepine.

Multiple Sclerosis:

Multiple sclerosis (MS) is a chronic disease characterized by inflammation, demyelination, gliosis (scarring) and neuronal loss; the course can be relapsing remitting or progressive. MS effects in 350,000 individuals in the USA and 2.5 million individuals worldwide [106].

Pain is a common symptom of MS, experienced by >50% of patients. Pain can occur anywhere on the body and can change locations over time [106]. Sensory symptoms are varied and include both paresthesias (e.g., tingling, prickling, sensations, formications, pins and needles or painful burning) and hypesthesias (e.g., reduced sensations, numbness or dead feeling). Patients also suffer from optic neuritis presenting sometimes as periorbital pain (aggravated by eye movement) [106, 107]. *Lhermitte's symptom* is an electric shock like sensation (typically induced by flexion or other movements of the neck) that radiates down the back onto the legs [106]. Trigeminal neuralgia (tic douloureux) can also occur in MS, when the demyelinating lesion involves the root entry (or exit) zone of the fifth cranial nerve. Pain in MS is always a troublesome issue

and needs a concrete pharmacotherapeutic intervention for its amelioration.

Khan [104] and Solaro et al. [105] reported the beneficial effects of GBP in 7 and 11 patients, respectively suffering from trigeminal neuralgia associated with MS that was refractory to previous therapies, or whose treatment was interrupted by side effects. A double blind, placebo controlled, crossover study on 21 patients using a 6 day dose titration upto 900mg of GBP *tid* or placebo, with a 14 day washout period was conducted by cutter et al., [107]. A reduction in spasticity compared with placebo, without adverse effects were shown. This study is in conformity with the study done by Mueller et al., [108] who showed statistically significant improvements in spasticity and disability in MS patients on GBP doses of only 400mg *tid*. Houtchens et al., [109] in an open label study in 25 MS patients with pain that was resistant to conventional therapies, evaluated the effectiveness of GBP with dose range of 300-2400mg/day. It was found that 31.8% of patients experienced excellent pain relief and another 36.3% reported moderate pain relief from throbbing pains, pins and needles and cramping pains, dull aching pains were the least responsive.

In an another open label trial Solaro et al., [110] successfully treated nocturnal spasms in 20/22 MS patients with low dose (up to 600mg per day) GBP. A larger, double blinded, placebo controlled trial is required to study the value of GBP in MS.

Complex regional pain syndrome (CRPS)

CRPS are an important group of painful conditions that may follow injury to bone, soft tissue and nerve tissue, characterized by serve burning pain, hyperpathia, allodynia, vasomotor and sudomotor changes, oedema, stiffness and discolouration and may progress to fixed trophic changes of untreated [111, 112].

Further, the burning pain that may follow within minutes or hours of the injury is often out of proportion to the original injury, and many other symptoms can develop to involve areas beyond the area of original injury sometimes even to the opposite extremity in one of the study conducted by Mellick and Mellick [113] on 9 patients with refractory CRPS who had previously undergone a variety of procedures (including stellate ganglion and lumbar sympathetic blocks) as well as other during therapy. Patients were put on 900-2400mg per day of GBP over 2-6 months with an excellent pain relief. Wheeler et al., [114] reported the successful use of GBP for the treatments of CRPS in the pediatric population.

HIV Neuropathy

Neuropathic pain related to acquired immunodeficiency syndrome was treated with GBP in addition to antiretroviral medication, and GBP demonstrated partial efficacy in this condition as well [115]. Gatti et al., [116] reported significant reduction in pain in eight patients with confirmed diagnosis of distal symmetric axonopathy treated with GBP (2000 and 2400mg per day). Newshan et al., [117] reported the efficacy of GBP in three patients with HIV suffering from distal sensory polyneuropathy.

Peripheral nerve injury and neuropathy

Damage to, or entrapment of nerves can cause pain, unpleasant sensation and paresthesias. Tricyclic antidepressants and GBP have been used with some success to treat neuropathic pain [118].

Spinal injury

Partial and complete spinal cord lesions are always associated with pain. Central dysaesthetic pain following spinal cord injury is often refractory to conventional treatment [119]. GBP has been reported to reduce central pain [120] and spasms associated with spinal cord injury [121].

Gabapentin: a potential multimodal perioperative drug

During the last 5 years a lot of research has been done in the field of anesthesia to explore the multimodal effects of GBP. These research works have arrived at various conclusions in evaluating the potential roles of GBP for post operative analgesia, preoperative anxiolysis, prevention of chronic post-surgical pain (CPSP), attenuation of hemodynamic response to direct laryngoscopy and intubation, prevention of postoperative nausea and vomiting (PONV) and postoperative delirium.

Postoperative analgesia

A systemic review of randomized clinical trials of GBP and pregabalin for acute postoperative pain relief [122] involving a total of 663 patients from seven original randomized placebo-controlled trials, when the patients from the pregabalin studies were excluded [123-129]

There were 333 subjects who received oral GBP and 330 who received placebo. Three outcome measures (postoperative opoid requirements, pain score at rest and pain score during activity) were compared between GBP and placebo groups. GBP significantly reduced postoperative opoid requirement during the first 24 hours in six of the seven studies. The mean pain scores at rest and during activity, within 6 hours after surgery, were significantly reduced in three of seven and two of four studies, respectively.

Physiological recovery after surgery

In addition to optimal pain management GBP has beneficial effects on physiological recovery after surgery. Preoperative GBP significantly improved post operative peak expiratory flow rate (PEFR) compared with placebo on post operative days 1 and 2 ($p= 0.002$) after abdominal hysterectomy [130].

Perioperative GBP significantly improved forced vital capacity (FVC) and PEFR at 24 hours ($p=0.005$; $p=0.024$) and 48hours ($p=0.005$; $p=0.029$) after thoracotomy [131]. O_2 saturation at 24 hours after abdominal hysterectomy was significantly higher in patients having preoperative GBP when compared with placebo ($p<0.05$) [132]. GBP appears to enhance recovery of bowel function after lower abdominal surgery. Passage of flatus, return of bowel function and resumption of oral dietary intake occurred earlier after abdominal hysterectomy in patients receiving GBP compared with placebo ($p<0.001$) [133].

Preoperative GBP also improved early post operative knee mobilization (especially flexion) after arthroscopic anterior cruciate ligament repair ($p<0.05$) [134].

Prevention of Chronic Post Surgical Pain (CPSP)

CPSP is defined as persistent pain, which had developed after a surgical procedure of at least 2 months duration, where other causes such as continuing malignancy or chronic infection have been excluded [135]. Since CPSP has inflammatory and neuropathic [136] components involving peripheral and central sensitization [137] that arises in response to tissue and nerve injury. As GBP is effective across a wide spectrum of pain states, its efficacy in the prevention of CPSP has been investigated. A randomized study conducted by Nikolajsen et al., [138] on the effects of GBP on post amputation pain, arrived at the conclusion that GBP administration didn't reduce the incidence or intensity of postamputation stump and phantom pain. Although GBP has anti-hyperanalgesic effects [139, 140] there is no scientific evidence to support its use for the prevention of CPSP [141].

Attenuation of haemodynamic response to laryngoscopy and endotracheal intubation

The pressor response of tachycardia and hypertension to laryngoscopy and endotracheal intubation may increase perioperative morbidity and mortality, particularly for those patients with cardiovascular or cerebral disease [142, 143]. A variety of drugs have been used to control this hemodynamic response [144]. Two randomized placebo controlled trials [145, 146] supported the use of GBP in attenuating haemodynamic response to direct laryngoscopy and tracheal intubation.

Preventive role for Post Operative Nausea Vomiting (PONV)

PONV has always been a matter of great concern and challenge to anesthesia providers [147]. PONV are common after anesthesia and surgery with an overall incidence of 25-30% [148, 149, 150] and is also one of the most common reasons for poor patient satisfaction

ratings in the post operative period [151]. An open label preliminary study demonstrated the antiemetic effect of GBP in chemotherapy induced acute (within 24 hours) and delayed breast cancer [152]. Pandey et al., [153] in a study of 250 patients undergoing elective laparoscopic cholecystectomy found that pre operative single dose of 600mg oral GBP reduced the incidence of PONV in 60% of patients compared to placebo where the incidence was 37.8% ($p=0.04$). Rosarius et al., [154] used GBP 1200mg orally preoperative to prevent post operative pain after vaginal hysterectomy and in addition to its post operative analgesic effect a tendency towards a lower incidence of PONV was observed although statistically insignificant. Turan et al., [155] studied the use of oral GBP given preoperatively in patients of spinal surgery noticed significant reduction in incidence of vomiting ($p<0.05$) compared to placebo. The mechanism of GBP in the prevention of PONV is unknown but it could possibly be due to the indirect effect of opoid sparing or a direct effect on tachykinin actively [156] Mitigating of tachykinin neurotransmitter activity by GBP has been a postulated mechanism [141]. In order to yield the desirable postoperative results GBP as a potential multimodal perioperative drug could be given in the dose of 900mg, one to two hours before surgery [141].

Gabapentin: Clinical Efficacy in Restless Leg Syndrome (RLS)

RLS is a sleep related movement disorder which involves an unpleasant urge to move the limbs, typically the legs to relieve the symptoms. RLS symptoms are usually present or worsen in the evening [157]. RLS is a common, distressing disease that affects a significant percentage of the adult population. In the US, 2% to 3% of the population experiences clinically bothersome symptoms severe enough to warrant treatment [158-160]. GBP has also been shown effective in improving RLS symptoms reducing the frequency of periodic leg movements and improving sleep quality, suggesting a potential role in treating RLS [161-165]. GBP is not approved for the indication of RLS treatment, although it is often used off-label for this purpose [166-168].

In view of the pharmacokinetic limitations of GBP Cundy and coworkers at Xenopart Inc. designed a compound which was designated as gabapentin enacarbil or XP13512 [169].(fig. 2) Gabapentin enacarbil is a GBP prodrug. It is an acyloxyalkylcarbamate analog with an efficient enzymatic conversion to yield GBP *in vivo*. GBP enacarbil is administered as an oral formulation. Two formulations for the use in RLS has been evaluated immediate release (IR) and extended release (XR) formulation [170, 171]. Clinical trials have shown GBP enacarbil to be safe and effective drug for RLS [172 - 174]. An application of GBP enacarbil for treatment of RLS is currently pending with FDA for approval.

Gabapentin: Role in the treatment of Hot flashes in post menopausal women

Natural menopause is often associated with a clustering of symptoms under the colloquial term "hot flashes" (also referred to as "hot flushes") [175]. Hot flashes usually involve a rapid onset reddening of the skin on the chest, neck and head along with a perception of increased body heat [176, 177]. These symptoms might be accompanied or followed by perspiration, palpitations, irritability and anxiety [176, 177]. Approximately 70% of the post menopausal women have experienced hot flashes for an average of 0.5 to 5.0 years after menopause. For ~10% of post menopausal women, the symptoms may last upto 15 years [176]. Similarly, women who have been receiving antiestrogen therapy (primary tamoxifen) for breast cancer have reported hot flashes [178]. Despite the significant prevalence (70%) of hot flashes [176] and their non negligible duration, current treatment modalities are limited. Hormone replacement therapy (e.g., estrogen) has been shown to be effective [179], however, adverse events and breast cancer, even if not unanimously accepted [180], could raise important concerns about its use [181] and potentially limit the target group that is suitable for treatment. Several non hormonal agents, including GBP, antidepressants, clonidine, methyldopa and isoflavone extracts have been used for the treatment of hot flashes. Beneficial reports have been reported for SSRI [182, 183], SNRI [184] and GBP [185-187].

A good amount of work has been done to see the efficacy and tolerability of GBP on different doses in the treatment of hot flashes in post menopausal women. Toulis et. al., [188] performed a systematic review and meta-analysis of seven trials [185-187, 189-192] conducted in 901 patients between 2002 and 2008. Study sizes ranged from 222 to 420 patients, total daily doses of GBP ranged from 900 to 2400mg and titration periods lasted 3 to 12 days. All these trials were conducted separately reporting on the efficacy and tolerability of GBP in women with hot flashes. They reported reductions of 20% to 30% in the frequency and severity of hot flashes with GBP as compared to placebo, although the data across the studies were too heterogeneous to provide a reliable summary effect. Clusterings of dizziness/unsteadiness and fatigue/somnolence were the most frequently reported adverse events associated with GBP and resulted in a higher dropout rate due to adverse events in the GBP treated patients than in the controls. More studies are needed to consolidate the outcomes and elucidate the useful details regarding this treatment.

Gabapentin: Efficacy in Migraine prophylaxis

Migraine, the second most common cause of headache, afflicts approximately 15% of women and 6% of men over a one year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound or movement; nausea and vomiting often accompany the headache [193]. Medication used in migraine prophylaxis comes from different pharmacological classes and most have primary indications for the other medical conditions [194-196]. Beta blockers and tricyclic antidepressants have been often used as first line therapy for migraine prevention. Other preventive drugs include pizotifen, flunarizine and methysergide [197]. However, in some patients where these medications are contraindicated or that suffer from co morbid diseases, anti-epileptic drugs (AEDs) may be offered as an appropriate first line prophylactic treatment. GBP is among AEDs that have been evaluated for efficacy in migraine and cluster headache prevention [198-202].

Vokovie et. al., [203] performed an open label study to evaluate the efficacy and safety of GBP in the prophylaxis of migraine in which daily doses of 900 – 1800mg GBP resulted in a significant mean reduction of migraine days, reduction in pain intensity and in the use of acute medications. Although adverse events occurred in a relatively high percentage, the treatment with GBP was safe and well tolerated in the majority of patients. Although not approved by FDA, but GBP in the dose range of 900-3600mg per day has displayed prophylactic efficacy in the treatment of migraine [193]. In addition to aforementioned uses of GBP it has also proved its efficacy in treatment of essential tremor [204-207] and bipolar disorder [208].

Table 1: Frequency of adverse events being reported in the controlled clinical trials with the addition of either GBP or Placebo

S. No.	Effect	Gabapentin (%)	Placebo (%)
1	Somnolence	20	9
2	Dizziness	18	7
3	Ataxia	13	6
4	Fatigue	11	5
5	Tremor	7	3
6	Diplopia	6	2

Table 2: Examples of causes of neuropathic pain

Trauma	Phantom Limb; Peripheral nerve injury; Spinal cord Injury; Post Traumatic neuralgia; Surgical; Complex regional pain syndrome (CRPS)
Infection/Inflammation	Post herpetic neuralgia; HIV; Pain associated with Guillain Barre Syndrome
Compression	Trigeminal Neuralgia; Sciatica; Carpal tunnel Syndrome
Cancer	Invasion/ compression of nerve/tissue by tumor
Ischaemia	Post stroke pain; metabolic neuropathies e.g., diabetic peripheral neuropathy; Spinal Ischaemic pain
Demyelination	Multiple sclerosis
Drugs	Vinca alkaloids; Ethanol; Taxols; Anti bacterials for TB and HIV
Nutritional Deficiency	Polyneuropathy due to B_{12} deficiency

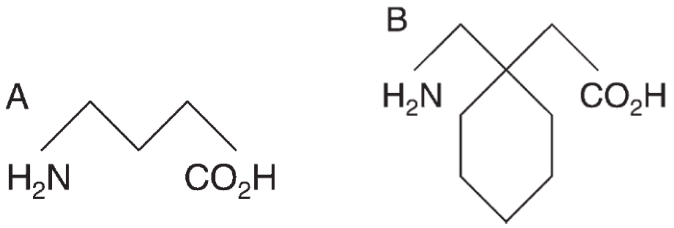

Fig. 1: The structural formulae of GABA (A) and gabapentin (B).

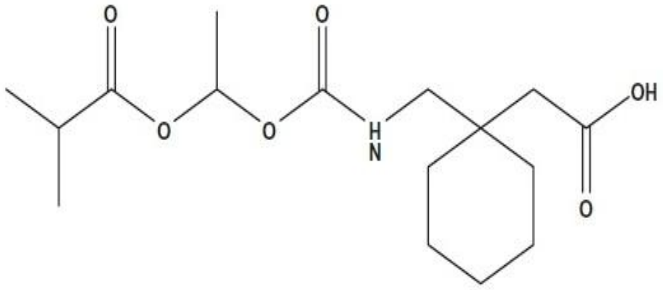

Fig. 2: Chemical structure of gabapentin enacarbil

CONCLUSION

GBP has been an all time a block buster drug. According to a recent survey in the USA, GBP had the highest proportion of off-label prescription (83%) among 160 commonly prescribed drugs; where only less than 20% of its off-label use had strong scientific evidence of clinical efficacy [209]. GBP drew substantial media attention, because its manufacturer was convicted and investigated for inappropriate marketing of off-label uses of the drug [210] and for inappropriate promotion of unapproved uses for GBP [211, 212]. More studies are needed to consolidate the outcomes and elucidate useful details regarding the various pharmacotherapeutics effects of GBP.

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