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Review Article

Gabapentin: An update of its pharmacological properties and therapeutic use in epilepsy

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Abstract

The new antiepileptic medications are prescribed for the treatment of patients with seizure disorders since 17 years ago. Gabapentin (GBP) was approved on January 1994 as adjunctive treatment in patients 12 years or older with partial seizures, with or devoid of secondary generalization. GBP, was formerly known as an anticonvulsant γ-aminobutyric acid (GABA) mimetic, is considered as a safe and well-tolerated antiepileptic drug (AED) with promising pharmacokinetic properties and a wide therapeutic index. GBP is useful for the therapy of mixed seizure disorders and refractory partial seizures in children. GBP must be regarded as the first treatment for older patients with recently diagnosed seizures. GBP has a well recognized clinical efficacy in those types of focal epilepsy which were resistant to the traditional AEDs. The main object of this review was to evaluate the efficacy, tolerability, dosing schedules and safety of GBP that have been investigated in peer-reviewed journals.

KEYWORDS: Antiepileptic drugs, efficacy, epilepsy, gabapentin, new antiepileptic drugs, seizures.

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Approximately 2 million people in the United States suffer epilepsy.[1] Besides to its medical influence, epilepsy has extensive psychosocia1[2] and economic outcomes.[3] Successful seizure control is very important in decreasing the psychosocial and economic costs of epilepsy. Nevertheless, most therapies didn't completely improve patients for numerous reasons. In some cases, the chosen antiepileptic drug (AED) is unsuitable for the patient's seizure type. In the other cases, therapy with AED is discarded since the drug was prescribed at sub-therapeutic doses that did not complete therapy or at extremely excessive initial doses that resulted in significant adverse reactions.[4] The new AED including gabapentin have broad spectrum of antiseizure effects, less adverse effects and less drug interaction.[4]

Of the older AEDs, carbamazepine and valproate together bring a threat of hepatic toxicity and have been associated with fetal anomalies.[5] Carbamazepine and phenytoin aggravate hypersensitivity reactions in a significant number of patients, and phenytoin is associated with chronic adverse events (AEs).[5,6] Four of the six AEDs (phenytoin, carbamazepine, phenobarbital, and primidone) are hepatic enzyme inducers.[7] Valproic acid, on the contrary, is a powerful hepatic inhibitor.[8] The newer agents have fewer drug interactions and slight, if at all, effect on the CYP450 enzyme system and other metabolic pathways. One of these new agents was gabapentin (GBP).[9] GBP has since achieved international acknowledgment, not for its antiepileptic properties, but also its effectiveness in the managing of acute and chronic pain syndromes, especially neuropathic pain.[9] It is prescribed as an add-on medication for the treatment of patients aged >12 years with partial and secondary generalized tonic-clonic seizures and for children aged 3 to

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12 years with partial seizures.[10] It has been used for monotherapy in adults in 38 countries out of the United States. Gabapentin is regarded as safe and tolerable with a promising pharmacokinetic profile and an extensive therapeutic index.[10] Also, gabapentin have been approved in Japan as adjunctive drug therapy for medically intractable seizures.[4]

The present article reviews the available information that dealing with the long-standing efficiency and safety of gabapentin in the treatment of patients with epilepsy.

Gabapentin chemistry and pharmacokinetics

As a drug, gabapentin was formerly considered as a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). However, preliminary studies proposed that gabapentin did not bind to either GABA-A or GABA-B receptors[11], nor was it transform metabolically into GABA.[12]

GBP also prevents voltage-dependent sodium currents.[13,14] GBP is properly absorbed subsequent to the oral administration.[15] GBP is not metabolized in human beings. It does not induce hepatic microsomal enzymes. It has no plasma protein binding and no interfaces with other drugs. GBP is more than 95% excreted unchanged in urine. The anticonvulsant effect can be obtained fairly quickly.[16] A three times in a day (TID) schedule has been advocated,[17] but in patients in whom the drug has a long half-life, two times in a day (BID) administration perhaps is adequate. Pediatric subjects aged > 1 month and < 5 years attained ~ 30% less exposures than that experienced in those aged ≥ 5 years. Nevertheless, in renally compromised patients, the half-life may be considerably longer.[18] Since gabapentin is not bound to plasma proteins, there is no competition with other extremely protein-bound medications, for example phenytoin.[19] As well, the lack of hepatic metabolism or induction/inhibition of hepatic drug metabolizing enzyme systems (cytochrome P450) or uridinediphosphoglucuronyl transferase isozymes by gabapentin abolishes interactions with other hepatically cleared medications, for instance older AEDs.[20] Adverse effects were commonly mild in intensity and included somnolence, dizziness, ataxia, nystagmus, diplopia, and tremor.

Clinical experience with gabapentin

Ranking of potentially appropriate studies

All important studies were judged for their Class of Evidence derived from principle modified from the United States Agency for Health Care and Policy Research[21] and the American Academy of Neurology[22] scoring systems.

Partial epilepsy

There were only some studies with class I evidence that assessed the effectiveness of gabapentin in patients with intractable partial seizures.[23] Doses experienced varied from 600 mg/day to 1,800 mg/day.[24] Rajna P and Szijarto E[25] acknowledged the efficiency and safety of gabapentin (GBP) in idiopathic or crypto/symptomatic partial epilepsy in adults. Marson AG and colleagues[26] showed that gabapentin has efficiency as an add-on therapy in patients with drug-resistant partial epilepsy. Herranz JL[27] concluded that GBP is an efficient drug which is well tolerated by children and adolescents with partial epilepsy, when employed in polytherapy or as monotherapy. Sancho-Rieger J and López-Trigo J[28] showed that gabapentin is an efficient, favorably tolerated drug utilized as monotherapy in partial epilepsy. Delahoy and colleagues[29] showed that in patients with refractory partial epilepsy, pregabalin was more effective than gabapentin on clinical response and the number of seizure-free days over the last 28 days.

Generalized epilepsy

Generalized epilepsy syndromes are classified as idiopathic or symptomatic. Idiopathic epilepsy, as well called 1° generalized epilepsy, has genetic base in the setting of normal brain structural. Seizure types are limited to myoclonic seizures, generalized tonic-clonic convulsions (GTCs), and absence (petit mal). In contrast, symptomatic epilepsy, as well called

2° generalized, is a destructive type of epilepsy in which developmental anomaly exists, and a structural defect is recognized. One of the more frequent symptomatic epilepsy syndromes is the Lennox-Gastaut syndrome, described by mental retardation, multiple seizure types, and distinctive EEG pattern of slow spike-wave. Evidence for efficiency of the newer AED in the generalized epilepsy syndromes is not as promptly obtainable as evidence in the partial syndromes. A great majority of the existing information are class IV.

Idiopathic generalized epilepsy in adults

In a research was done by Platt SR and colleagues[30] on eleven dogs with refractory idiopathic epilepsy, they showed that addition of gabapentin to mixture of phenobarbital and potassium bromide at doses enough to attain satisfactory therapeutic serum levels caused both the number of seizures per week and the number of days with any seizures in a one-week period significantly decrease. Mild side effects of ataxia and sedation were noted in five of the dogs, but they were not severe adequate to merit the treatment being terminated. There is one article with class I evidence that evaluated the efficiency of gabapentin in refractory generalized tonic-clonic seizures in patients with primary or secondary generalized epilepsy[31] Additionally, there is one article with class I evidence and 4 with class IV evidence that considered efficacy in "combined" group of up to 361 generalized and partial epilepsy patients[32]

Treatment of refractory epilepsy in children

There is one double blind placebo-controlled trial study with class I evidence[33] that evaluated the efficiency of gabapentin in 247 children aged 3 to 12 years. Gabapentin was titrated equal to a dose of 23 to 35 mg/kg/day. There were no researches to assess that the new AEDs are successful in children and/or adults with the Lennox-Gastaut syndrome. One case series and one case report reported aggravation of myoclonic seizures in this population when they were treated with gabapentin.[34] There is one double-blind, placebo-controlled study with class I evidence[35] that evaluated the efficiency of gabapentin monotherapy in 33 children aged 4 to 12 years with newly diagnosed absence seizures. Somnolence and dizziness were the two most common side effects.

New onset geriatric epilepsy

Epidemiologic data indicates that the occurrence of epilepsy increase significantly after age 60.[36] Features complicating the treatment of seizures in older age groups consist of simultaneous medical diseases, polytherapy, alteration in pharmacokinetics (pK), and changed CNS pharmacodynamics.[37] Gabapentin seemed to have promising pharmacokinetics and side effect in elderly.[38,39] Complex partial seizures alone were the most frequent seizure type (43.2%). Only 25.3% presented with GTCs alone, a lesser amount than described in epidemiologic studies that principally comprise younger adults.[40] Gil-Nagel A[41] in a study of assessment of gabapentin in the treatment of epilepsy in the elderly showed that gabapentin 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.

Gabapentin effectiveness as initial monotherapy for epileptic seizures and syndromes

***Adults with partial-onset seizures*:** Derived from existing evidence, GBP is effective as initial monotherapy for adults with recently diagnosed or untreated partial-onset seizures.[38,42,43]

Children with partial-onset seizures: Either no information or insufficient data are available to make a decision whether GBP could be regarded as for initial monotherapy for children with newly diagnosed or untreated partial-onset seizures.

Elderly adults with partial-onset seizures: A scarcity of class I and class II randomized controlled trials (RCTs) be present for elderly

adults with partial onset seizures. GBP was shown effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures.[44]

Adults with generalized-onset tonic–clonic seizures: According to RCTs efficacy and effectiveness evidence, GBP is possibly efficacious/effective as initial monotherapy for adults with generalized onset tonic–clonic seizures.[45-47]

Children with generalized-onset tonic–clonic seizures: Either no data or insufficient efficacy or effectiveness data are available to determine whether GBP could be prescribed for initial monotherapy for children with newly diagnosed or untreated GTC seizures.[42]

Children with absence seizures: Based on RCT efficacy and effectiveness evidence, GBP is an ineffective treatment for children with absence seizures.[43]

Children with benign epilepsy with centrotemporal spike (BECTS): Based on available efficacy and effectiveness evidence alone, GBP is possibly efficacious or effective as initial monotherapy for children with BECTS.

Juvenile myoclonic epilepsy: Class IV studies showed that GBP may trigger or exacerbate absence seizures, and myoclonic seizures.[43]

According to the USA guidline for epilepsy treatment, the patients with newly diagnosed epilepsy can be treated with gabapentin.[19]

Seizure in stroke patients

One of the complications of stroke in adults is epilepsy. Gabapentin and lamotrigine are the only two drugs that approved to be more effective than carbamazepine in elderly patients with stroke because they don't interact with anticoagulants and antiplatelet agents that are prescribed in these patients.[48]

Evaluation of serious, uncommon and long-term side effects

Oedema and myoclonic jerking could be a consequence of higher than suggested doses of GBP. Hyponatraemia might be an uncommon incident, and hair loss might be a lasting effect of GBP treatment, though not listed by the company. Cancers and infections experienced in a few patients were not absolutely related to GBP.[49]

Gastrointestinal (GI) discomforts are among the most common adverse effects of AEDs including gabapentin. Jahromi et al.[50] showed that when gabapentin was added to the other AEDs, the incidence of the occurrence of diarrhea, dysphagia, or heartburn was significantly increased. Also, addition of gabapentin to the other AEDs in multiple drug therapy was accompanied with the highest incidence of GI adverse effects. This may affect the effectiveness of the therapy with AEDs and increase the chance of further attacks.

Molgaard-Nielsen and colleagues[51] showed that first-trimester exposure to gabapentin compared with no exposure was not associated with an increased risk of major birth defects among live-born infants in Denmark.

Second-Generation Antiepileptic Drugs' Effect on Balance

Falls are described as an impulsive, accidental change in position that causes a person to put down at a lower level, on an object, or on the land.[52] Individuals who fall down are at high risk for hospitalization, nursing home admittance, disability, and death.[52] AEDs are also employed to treat disorders for instance migraine, neuropathic pain and other chronic pain circumstances, and psychiatric disorders[52] increasing the probability that individuals at risk of falling possibly will be rendered to these drugs.[53] These medications may possibly increase the risk of imbalance and accelerate the rate of bone loss, unwanted outcomes for all patients at risk of falls and fractures.[52] Felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin, and zonisamide ("second-generation" AEDs) have since been accepted for adjunctive treatment of partial epilepsy. A view is that these AEDs are better tolerated and safer than first-generation AEDs. Patients with epilepsy

have a 2- to 6-fold risk of skeletal fractures mainly because of falls.[54] In one research, less than half of the reported falls were directly assigned to a seizure.[55] Falls secondary to AED-related ataxia or disequilibrium may describe for a considerable percentage of the remaining fractures.[55] Only 2 AEDs, gabapentin and levetiracetam, were not related with an increased risk of ataxia or imbalance at any dose; nevertheless, the tendency was in the direction of a dose-response effect.

Herranz JL and Armijo JA presumed that for the association of antiepileptic drugs to increased efficiency without increase the level of toxicity, the hypothetical base of judicious combination therapy take into explanation the mechanism of action, the range, the safety, and the pharmacodynamic and pharmacokinetic interactions of each antiepileptic drug; the number of times the drug is taken is an additional factor to be taken into consideration. Assessment of the efficiency, safety, interactions and number of doses recommends the subsequent order, from more to less appropriate for combination therapy: levetiracetam/pregabalin > gabapentin > lamotrigine > oxcarbazepine/topiramate/zonisamide > tiagabine > valproic acid > carbamazepine > phenytoin > phenobarbital/primidone > benzodiazepines.[56]

Gabapentin offers successful antiepileptic treatment, confirmed to definitely affect seizure severity, concurrently not deteriorating any other factors (such as challenging behavior), and with their established safety profile, are unlikely to aggravate any other problems. Adverse effects with gabapentin were mainly limited to the titration phase, and once the maintenance dose was achieved, fewer problems were noticed. On the base of the results of the above mentioned trials, there is currently growing proof to hold the effectiveness of GBP as monotherapy for the treatment of partial-onset seizures.[57,58] The exit task is to identify specific patient populations with partial epilepsy in whom the pharmacokinetic and/or safety profile of GBP would make it a desirable alternative as monotherapy. Some of those populations contain patients with porphyria, hepatic disease, elderly patients receiving polytherapy, children with benign partial epilepsies of childhood, and patients receiving immunosuppressants. For instance, there is now proof, derived from cell cultures and clinical reports, that GBP does not increase porphyrin production in patients with porphyrias, make up it a first-line agent for the treatment of seizures in these disorders. Additionally, GBP is the only AED, excluding vigabatrin, that is not hepatically metabolized, and it would consequently be extremely helpful as monotherapy for patients with seizures and liver disease. Seizures in the elderly are commonly simply controlled, but patients in this age group are much more sensitive to the adverse events of AEDs. Elderly patients also are apt to receiving a number of prescription medications, many of which are metabolized in the liver and can lead to significant drug-drug interactions in the existence of AEDs that have a tendency to provoke or prevent hepatic microsomal enzymes.[36,57-58] The safety of GBP and its lack of drug-drug interactions make it a very desirable choice in this patient population. Its lack of drug-drug interaction is also a benefit in patients with partial seizures who are getting simultaneous treatment with immunosuppressive drugs.[59-62] No trials have been performed in newly diagnosed patients with any idiopathic generalized syndrome. This must be carried out in patients with idiopathic generalized tonic-clonic seizures and juvenile myoclonic epilepsy, who immediately require more AED alternatives. While new AEDs may have some attractive characteristics, they are much more costly than standard drugs. Future investigation using economic decision analysis would assist to reveal whether the possible benefits are worth the added cost. This would consist of studies on the clinical significance of hepatic enzyme induction, changes in hormonal milieu, and long-term adverse effects. Lastly, future studies should utilize extended release formulations every time probable. Studies employing cognitive outcome measures should apply more strict testing protocols, which deem

practice effects, and the probable effects of emotional state on cognitive functioning.

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Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
AH has planned the review article and finalized it; MRS and MZ have planned the review article and finalized it too; AH and MRS did the evaluation statistical analysis and prepared the first version of review article and revised the final version for publishing. All authors read and approved the final review article.

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