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Review

A Comparative overview of Older Vs Newer Antiepileptic Medications (AEDs)

Vishakha Kaintura*[1], Ujjwal Pundir[1], Shristi Pundir[1], Shaffi Tangri[2], Divya Juyal[3]

[1]*Intern, Pharm. D., School of Pharmaceutical Sciences, Shri Guru Ram Rai University*
[2]*Assistant Professor, School of Pharmaceutical Sciences, Shri Guru Ram Rai University*
[3]*Professor, School of Pharmaceutical Sciences, Shri Guru Ram Rai University*

Corresponding Author:
Vishakha Kaintura

Email:
kainturavishakha@gmail.com

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Abstract:
For many years, antiepileptic medications (AEDs) have been the mainstay of epilepsy treatment. Although they are well-established in clinical practice, older AEDs like phenytoin, carbamazepine, and valproate have a number of limitations. These include complex pharmacokinetic interactions brought on by enzyme stimulation, a greater risk of teratogenicity, bone loss, and neuropsychiatric adverse effects. On the other hand, more recent AEDs with better safety profiles include levetiracetam, lamotrigine, oxcarbazepine, and lacosamide. They are less likely to cause drug-drug interactions, have fewer negative effects on cognition and psychiatry, and are typically better tolerated. These benefits make them especially appropriate for older people and those who need polypharmacy due to comorbidities. Newer AEDs frequently have higher prices and less long-term safety evidence, despite these advantages. For example, levetiracetam is an effective medication, but dosing tactics might affect its acceptability; slower titration and lower doses reduce adverse effects.

Keywords: Epilepsy, AEDs, neurological, Brain, antiepileptic

INTRODUCTION

A chronic neurological condition called epilepsy is characterized by frequent, spontaneous seizures. Over 50 million individuals worldwide suffer from epilepsy. Between 4.15 to 7.03 percent people per 1000 are affected by epilepsy in India.

Moreover, it was felt that there remains considerable scope for the development of better epilepsy services in a developing country like India.(1)

Furthermore, a huge number of these modern AEDs are prohibitively expensive and many of them are recently introduced to the Indian market.(2)

It can be difficult to choose the best antiepileptic medication (AED) for a patient. The three primary criteria used by physicians when choosing a medication are safety, tolerability, and efficacy. While medication efficacy could be one of the most important factors to take into account, a drug's safety and tolerability may be the primary causes of a patient losing interest in and stopping a medication. Many patients had to pick between a life of seizures and unbearable medication side effects for years when there were only a few AEDs available. The newest generation of AEDs offered the promise of increased safety and fewer adverse events (AEs) in addition to increased efficacy.

A pharmaceutical that is easily absorbed, doesn't interfere with or change the metabolism of other drugs, can be used once daily, and reaches a steady state in one or two doses would be ideal. With such a medication, undesirable, superfluous effects would be avoided by acting selectively at a particular neural receptor. It would not produce systemic or central nervous system (CNS) toxicities, nor would it have any undesirable side effects. Patients would tolerate the medication very well.

There are two techniques to compare antiepileptic medications. The first step is to determine which adverse events (AEs) happened in randomized, placebo-controlled add-on trials comparing one medication to another. Comparing new and old medicines in this way is challenging since different

methodologies were used for randomized trials when the older drugs were undergoing clinical testing. Another approach is to directly compare the new medication with an old treatment in a randomized head-to-head trial.

Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are some of the novel AEDs that have been created recently that combine great efficacy with a low incidence of side effects. Children with intractable epilepsy are treated with these more recent AEDs in addition to traditional AEDs.

Furthermore, a huge number of these modern AEDs are prohibitively expensive and many of them are recently introduced to the Indian market.[3]

Specific AED adverse effects and safety profiles: New versus Old

Phenytoin, introduced in 1938 and formally approved by the US Food and Drug Administration (FDA) in 1953, phenytoin is well-known for its number of adverse effects on the central nervous system (CNS) and other organ systems, such as nystagmus, ataxia, diplopia, drowsiness, impaired concentration, gingival hyperplasia, hirsutism, acne, hepatotoxicity, and idiosyncratic reactions with aplastic anemia and lupus-like reactions.[3,4]

When ethosuximide was first put on the market in 1960, its use as a treatment for absence epilepsy was rather limited. Its adverse event profile consists of a variety of idiosyncratic reactions as well as nausea, anorexia, abdominal pain, sleepiness, and dizziness.[5]

In 1974, carbamazepine was first made available. Sleepiness, dizziness, loss of coordination, and weight gain are typical adverse events (AEs).[6,7] There have also been reports of idiosyncratic reactions, rash, hyponatremia, leucopenia, and rare occurrences of hepatotoxicity.[8]

Since its introduction to the market in 1978, valproate has been linked to a number of side effects, some of the more severe and/or common ones include dose-related tremor (which is less common with controlled-release formulations), hair loss, weight gain, nausea, vomiting, hepatotoxicity, acute hemorrhagic pancreatitis, thrombocytopenia, and hyperammonemia; lethargy has also been reported, though it is less common.[9]

Valproate is also associated with the greatest risk for major congenital malformations (MCMs) among the existing AEDs[10].

Lamotrigine

Three studies were examined: one compared the safety and effectiveness of lamotrigine (titrated to 150 mg/day) against immediate-release carbamazepine (titrated to 600 mg/day) another examined the safety and effectiveness of lamotrigine (maximum dose of 500 mg/day) in elderly patients receiving immediate-release carbamazepine (maximum dose of 2000 mg/day) and the third examined the comparison between lamotrigine (dosed between 150–400 mg/day) and phenytoin (dosed at 300–600 mg/day).[11,12,13]

In the two studies comparing lamotrigine with carbamazepine, it was shown that a greater proportion of patients discontinued their medication due to side effects, and one study discovered a markedly higher incidence of rash in the carbamazepine-treated group.[14] The lamotrigine versus phenytoin trial, interestingly, revealed a fairly similar discontinuation rate in each therapy group as a result of adverse events (AEs); nevertheless, asthenia, somnolence, and ataxia were more common in the phenytoin-treated group. Rash happened more often in the group that took lamotrigine. Hepatotoxicity is not known to be caused by lamotrigine.

Topiramate

A study examined the effectiveness and safety of various dosages of topiramate (100 and 200 mg/day) in comparison to valproate (1250 mg/day) and carbamazepine (600 mg/day). Depending on the dose used, discontinuation rates from topiramate ranged from 19% to 28%, valproate from 23% to 25%, and carbamazepine from 25% to 28%. These rates were comparatively similar for the three medications.[15]

Blood dyscrasias are unrelated to topiramate. There have been reports of rare cases of hepatic failure, especially when valproate is used concurrently.[16] Renal calculi are the most frequent idiosyncratic adverse event linked to topiramate use, occurring in 1.5% of patients with chronic use.[17] Paresthesias, hypohydrosis (particularly in youngsters), and metabolic acidosis are other adverse effects. Dose-dependent cognitive impairment, such as trouble remembering and naming things, can happen.[18]

Oxcarbazepine

There were three class I studies and one class II study that compared oxcarbazepine with older

AEDs. The first study, compared oxcarbazepine (600–2100 mg/day) with phenytoin (100–560 mg/day);[19] the second study, compared oxcarbazepine (600–2400 mg/day) with valproate (600–2700 mg/day);[20] the third study, compared oxcarbazepine (300–1800 mg/day) with immediate-release carbamazepine (300–1400 mg/day); [21] and the fourth study, compared oxcarbazepine (100–1350 mg/day) with phenytoin (100–400 mg/day) in children and adolescents[22]. Both the oxcarbazepine versus immediate-release carbamazepine trial and the studies comparing oxcarbazepine with phenytoin found that oxcarbazepine was better tolerated, with reduced discontinuation rates among the oxcarbazepine-treated groups. On the other hand, in the oxcarbazepine versus valproate research, there were no differences in discontinuation due to adverse events. The following are a few of the more typical adverse events (AEs) linked to oxcarbazepine: ataxia, lethargy, headache, dizziness, nausea, vomiting, rash, and others.[23] The usage of oxycodone has also been linked to a number of safety concerns, such as Stevens Johnson syndrome, allergic rash, and hyponatremia (of which 2.7% of patients had a blood sodium level of less than 125 mmol/L).[24]

Levetiracetam

The meta-analysis comprised three class I investigations (one monotherapy study, two add-on studies.[25] Levetiracetam (doses ranging from 1000 to 3000 mg/day) discontinuations owing to adverse events (AEs) varied from 7% to 13% (in contrast to a 5-8% discontinuation rate for placebos); however, the incidence of discontinuation was not correlated with levetiracetam dosage.[9] However, higher rates of asthenia and somnolence were observed on the higher dose of drug in a different research that started levetiracetam at high doses (2000 or 4000 mg/day) without titration.[26] Overall, the most commonly reported adverse events (AEs) were dizziness, somnolence, asthenia, headache, and infection; behavioural issues, depression, and psychosis were also mentioned.[9]

Levetiracetam, administered at 500–3000 mg/day, was related to significantly fewer early adverse events (AEs) and a higher 1-year retention rate when compared to phenytoin, which was dosed at 200–800 mg/day in a different study evaluating efficacy and tolerability in patients who had undergone supratentorial neurosurgery.[27]Levetiracetam and other second-generation AEDs were indirectly compared in a recent meta-analysis that gathered information from trials included in the Cochrane Library 2002.[28] The study conducted found that levetiracetam, when dosed between 1000 and 4000 mg/day, was as well tolerated as lamotrigine (75–400 mg/day) and gabapentin (600–1800 mg/day). Additionally, it showed a lower withdrawal rate compared to topiramate (200–1000 mg/day) and oxcarbazepine (600–2400 mg/day). In general, levetiracetam did not differ significantly from tiagabine (16–56 mg/day) and zonisamide (100–400 mg/day), with favorable withdrawal rate trends. In a more recent randomized double-blind experiment, levetiracetam at doses ranging from 500 mg twice day to 1500 mg twice day was compared to 400 mg to 1200 mg of controlled release carbamazepine per day, with dosages based on patient response. The two medicines had nearly the same dropout rates. Patients assigned to levetiracetam had depression and insomnia more frequently, while patients randomized to controlled release carbamazepine experienced back pain more frequently. Carbamazepine caused a somewhat greater rate of weight gain.

Gabapentin

When comparing three different gabapentin doses (300, 900, and 1800 mg/day) with a 600 mg/day dose of carbamazepine. The patients who received carbamazepine-treated gabapentin had a higher discontinuation rate owing to adverse events (AEs), with fatigue, somnolence, and dizziness being more common in the carbamazepine-treated group.[29]

Tiagabin

Due to its uncommon correlation with nonconvulsive status epilepticus, tiagabine's application as an adjuvant therapy for partial epilepsy has been restricted.[30] As a whole, the drug is well-tolerated; the most frequent adverse events (AEs) are anxiety, asthenia, dizziness, amnesia, and abdominal discomfort.[31] The QSS and TTA meta-analysis included three studies that employed tiagabine doses ranging from 15 to 56 mg/day as add-on therapy for individuals with partial epilepsy.[32] Tiagabine adverse events (AEs) caused 8% to 20% of drug-using patients to discontinue their treatment, while placebo-using patients experienced 8 to 9% discontinuation rates.[9] According to French et al. (2004), dizziness, tremor, aberrant thinking, anxiousness, and abdominal

discomfort were the five most common adverse events (AEs).

Studies that were left out of the initial meta-analyses of QSS and TTA compared tiagabine more closely to other AEDs. Dodrill and colleagues conducted a head-to-head trial evaluating the effects of tiagabine (8–80 mg/day) vs carbamazepine (200–2000 mg/day) and phenytoin (60–1000 mg/day) on mood and cognition; no significant differences were seen among the three drugs.[33]

Zonisamide

The review included two class I placebo-controlled studies that compared zonisamide with placebo at dosages of 20 mg/kg in the Schmidt and colleagues study and 100, 200, and 400 mg/day in the Faught and colleagues research.[34] 10% of patients receiving zonisamide and placebo discontinued their treatment. The top five adverse events (AEs) that were recorded were fatigue, dizziness, somnolence, anorexia, and aberrant thinking; other AEs included rash, depression, and renal calculi.[9]

Not included in the original TTA and QQS report, a more recent investigation by Zaccara and Specchio analysed nine open-label studies in which patients received zonisamide as monotherapy or as an add-on for at least six months at doses ranging from 50 to 1100 mg/day. Anorexia, headache, nausea, and irritability were all frequently reported adverse events (AEs), with somnolence and dizziness accounting for between 4% and 24% of patients' discontinuations from the experimental medication.[35]

General concepts: old *versus* new AEDs:

In conclusion, the decision between older and newer AEDs should be made on an individual basis, even though the latter offer notable benefits in terms of safety and tolerability, particularly for particular patient categories. Therapy decisions must be guided by factors like cost, side effect profiles, efficacy, and patient-specific concerns.

Hepatic enzyme induction is one further way that newer AEDs differ from their older counterparts. Hepatic enzyme inducers include primidone, phenytoin, carbamazepine, and phenobarbital, whereas hepatic enzyme inhibitors include valproate. The idea that these effects have implications for safety because they disrupt body homeostasis has been reinforced by recent studies. When AEDs are used, there is a chance that this will raise cardiovascular risk (as measured by elevated serum lipids and C-reactive protein) and change sex steroids. Polycystic ovarian syndrome may be exacerbated by valproate-induced hepatic enzyme inhibition.[36]

One such factor that might set new AEDs apart from old is how they affect bone mineral density (BMD) and general bone health. It is known that the older generation AEDs, especially phenytoin, may have an impact on BMD.[37]

Pregnancy centers are currently gathering data regarding the potential teratogenic effects and risk of congenital malformations (CMs) associated with AED use. According to the findings of a systematic literature review, children born to epileptic mothers who received valproate monotherapy or polytherapy (two or more drugs) containing phenobarbital, phenytoin, or valproate had a significantly higher risk of developing cerebral malaria (CMs).[38]

Another significant worry associated with AED therapy during pregnancy is the possibility of teratogenic consequences and congenital malformations (CMs), for which several pregnancy registries are currently gathering information. The risk of CMs in children born to epileptic mothers was found to be significantly higher in those exposed to valproate monotherapy and polytherapy (two or more drugs) when the polytherapy combination included phenobarbital, phenytoin, or valproate, according to the results of one systematic literature review.[38]

However, pregnancy records have revealed remarkably minimal teratogenicity for carbamazepine, which was originally thought to be hazardous during pregnancy. It also compares favourably with newer medications, including lamotrigine, which was thought to be safer. It was even named the best medication for pregnant women in a recent editorial.[39]

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