

Current Concepts in the Management of Idiopathic Generalized Epilepsies

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Abstract

Idiopathic generalized epilepsies (IGEs) are a group of epilepsies characterized by an underlying genetic predisposition and a good response to antiseizure medicines (ASMs) in the majority of the patients. Of the various broad-spectrum ASMs, valproate is the most effective medicine for the control of seizures in IGEs. However, with the availability of many newer ASMs and evidence showing the high teratogenic potential of valproate, the choice of ASMs for IGEs has become increasingly difficult, especially in women of the child-bearing age group. In this article, we review the current evidence regarding the efficacy and safety of various ASMs in patients with IGEs and provide practical guidelines for choosing appropriate ASMs in various subgroups of patients with IGEs.

Keywords: Idiopathic generalized epilepsy, juvenile myoclonic epilepsy, levetiracetam, valproate

INTRODUCTION

Idiopathic generalized epilepsies (IGEs) are a group of epilepsies with a strong underlying genetic predisposition.^[1,2] IGEs make up one-fourth of all epilepsies and usually have onset at a young age. Seizures in the majority of the patients with IGEs are easily controlled but many of these patients require long-term, often lifelong, treatment. This makes the choice of antiseizure medicines (ASMs) in patients with IGEs particularly challenging as one needs to avoid long-term medicine-related side effects while maintaining effective seizure control. With the better delineation of the natural history of various IGE syndromes, availability of many newer ASMs, the discovery of newer facets to many older ASMs, and the new evidence regarding the differential effectiveness of various ASMs, the management of IGEs has undergone a significant change over the last few years. In this article, we review the current evidence for the management of various IGEs and suggest an overall approach for the management of IGEs.

NOMENCLATURE AND GENERAL FEATURES OF IGEs

In 2017, the International League Against Epilepsy (ILAE) proposed the term “genetic generalized epilepsies (GGEs)” to describe all types of generalized epilepsies with a presumed genetic basis.^[1,2] It also suggested that the older term IGEs should only be used to describe four well-established syndromes, namely childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures alone (GTCA).^[1] Subsequently, the Nosology Task Force of ILAE recognized that the group of GGEs is broad and IGEs can be recognized as a distinct subgroup of GGEs.^[3] The GGEs

group also includes certain rare syndromes such as eyelid myoclonia with absences and myoclonic absence epilepsy, which have different clinical features and prognosis.^[3,4] The present review is focused on the four IGE syndromes only.

IGEs have four types of seizures, either alone or in various combinations: Generalized tonic-clonic seizures (GTCS), absence seizures, myoclonic seizures, and myoclonic-tonic-clonic seizures. These epilepsies are classified by the predominant seizure type, age at onset, and to a certain extent by electroencephalogram (EEG) features [Table 1]. Seizures in patients with IGEs typically begin at an early age and are easy to control. While absences and myoclonic seizures can be quite frequent in untreated patients, GTCS are typically infrequent. Patients with IGEs have normal cognition, normal MRI, and no neurological deficits. EEG is usually abnormal in untreated patients and typically shows generalized, symmetrical, bisynchronous spike and wave discharges. However, a normal EEG does not exclude the diagnosis of IGEs in an otherwise typical clinical setting. The yield of EEG can be increased by

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obtaining a sleep-deprived EEG, a sleep EEG, and prolonged recordings. Diagnosis of IGEs is based on the typical seizure semiology, classical EEG features, and positive family history in selected patients. Many patients with GTCA have no other seizure types and have normal EEG which makes it difficult to confirm the diagnosis in such cases. It is important to inquire about the minor seizures such as absences and myoclonic jerks in all the patients with apparent GTCS as the wrong diagnosis is often the cause for the uncontrolled seizures in patients with IGEs.

PROBLEM OF EVIDENCE IN IGE TREATMENT

The majority of the evidence for the use of ASMs in the treatment of IGEs comes from personal experiences, uncontrolled case series, and unblinded randomized controlled trials. There are no class I or class II studies evaluating the efficacy of ASMs in patients with IGEs except in CAE.^[5-7] For regulatory purposes, a monotherapy indication for a particular ASM is granted only if it is shown to be superior to another treatment, either placebo or an active medicine, in a randomized controlled trial.^[8] Conducting a placebo-controlled monotherapy trial in patients with epilepsy is considered unethical while there is overall reluctance to conduct double-blind active control trials.^[5-8] As a rule, new ASMs are compared with a placebo in patients with uncontrolled focal epilepsies before being approved. As IGEs are much less common compared to focal epilepsies and the majority of the patients with IGEs are well controlled, it is difficult to enroll patients with IGEs in clinical trials. Secondly, drug trials typically include patients with generalized seizures which makes it likely that many patients with focal epilepsy and only generalized seizures will be included in the IGE arm. Hence, it is difficult to have patients with pure IGEs in large clinical trials. Lastly, the majority of the patients with IGEs have multiple seizure types while the primary outcomes in drug trials are restricted to one of the seizure types. Hence, it becomes difficult to evaluate the efficacy of one particular ASM for different seizure types. Despite these limitations, many pragmatic clinical trials have been undertaken in recent years in patients with IGEs that have helped in guiding the management of these patients.

COMMON PRINCIPLES IN THE MANAGEMENT OF IGEs

While the overall principles of management in patients with IGEs are similar to other epilepsies, certain treatment protocols are specific to IGEs.^[9,10] As the majority of the patients with IGEs have multiple seizure types, the chosen ASM should be effective for all types of seizures. Importantly, certain drugs especially those acting through sodium channel blockade can aggravate seizures in patients with IGEs [Table 2].^[11-13] These narrow-spectrum drugs, notably carbamazepine and phenytoin, can lead to worsening of seizure control in IGEs and are not recommended in these patients. Based on these observations, patients with IGEs or those with unclassified epilepsy are usually treated with broad-spectrum ASMs [Table 3]. Seizures

Table 1: General features of idiopathic generalized epilepsies

- Have underlying genetic predisposition
- Onset in early age, usually during childhood or adolescent age
- Infrequent generalized seizures
- Have absence, myoclonic, generalized tonic-clonic, and myoclonic-tonic-clonic seizures either in isolation or in various combinations
- Early morning seizure occurrence and evidence of photosensitivity in many patients
- Normal IQ and neurological examination
- EEG shows bilateral, symmetrical, and synchronous generalized spike-wave discharges
- EEG discharges are often precipitated by hyperventilation, photic stimulation, and eye closure
- Good response to antiseizure medicines in 80-90% of the patients

Table 2: Drugs that can worsen specific seizure types in patients with IGEs

Antiseizure medicine	Seizure type that can worsen	Can precipitate absence/myoclonic status epilepticus
Carbamazepine	Absence, myoclonus	Yes
Phenytoin	Absence, myoclonus	Yes
Ethosuximide*	GTCS	No
Phenobarbitone [#]	Absence	No
Clonazepam/Clobazam [#]	Absence	No
Gabapentin	Myoclonus, absence	No
Vigabatrin	Myoclonus, absence	Yes
Tiagabine	Myoclonus, absence	Yes
Lamotrigine	Myoclonus	No
Levetiracetam [#]	Absence	No

*Probably related to ineffectiveness of ethosuximide against generalized tonic-clonic seizures. [#]Single case reports; not replicated. GTCS: Generalized tonic-clonic seizure

Table 3: Drugs useful and to be avoided in patients with IGEs

Broad-spectrum ASMs useful in IGEs	Narrow-spectrum ASMs to be avoided in IGEs
Valproate	Carbamazepine
Lamotrigine (can worsen myoclonus)	Oxcarbazepine
Levetiracetam/Brivaracetam	Phenytoin
Topiramate	Gabapentin/Pregabalin
Zonisamide	Vigabatrin
Clobazam	
Perampanel	
Phenobarbitone	

ASMs: antiseizure medicines; IGEs: idiopathic generalized epilepsies

in the majority of the patients with IGEs can be controlled with small doses of appropriate ASMs and hence these patients should be initiated at low doses. Lastly, the majority of the patients with IGEs, except CAE, require long-term treatment. Hence, proper choice of an ASM and patient counseling is essential to avoid long-term side effects and to ensure compliance.

CURRENT EVIDENCE FOR ASM USE IN IGEs

As discussed above, no single ASM has class I or class II evidence of efficacy as initial monotherapy in patients with IGEs. The majority of the trials have included patients with IGEs without specifying the syndromes. Only a few studies have specifically studied the effectiveness of ASM in specific IGE syndromes.

ASMs in patients with IGEs

Many early observational studies in patients with IGEs established the efficacy of valproate in the management of these patients.^[14,15] With the realization that phenytoin and carbamazepine can aggravate myoclonic and absence seizures, valproate was considered as the drug of choice in patients with IGEs. After the availability of newer ASMs, many studies have reported the comparative efficacy of various ASMs in the treatment of IGEs. A large observational study, involving 962 patients with IGEs, reported 1-year seizure freedom in 54% of the patients.^[16] In this study, valproate was more effective (52%) as compared to topiramate (35%) and lamotrigine (17%). None of the patients in whom valproate was ineffective became seizure free with any other monotherapy. Of these patients with valproate-resistant seizures, 12% became seizure free with valproate and lamotrigine combination.^[16]

Subsequently, three major randomized trials have specifically examined the efficacy of various broad-spectrum ASMs in patients with IGEs. These trials have included patients with generalized seizures irrespective of the underlying syndrome. These randomized trials had a pragmatic open-label design wherein treating physicians decided the doses and treatment responses. Standard and New Antiepileptic Drugs (SANAD) trial was the first randomized nonblinded trial that recruited patients from outpatient clinics in the United Kingdom.^[17] Arm B of the trial randomized 716 patients with newly diagnosed generalized or unclassifiable epilepsy to receive valproate, lamotrigine, or topiramate. In the IGE subgroup, valproate was significantly better than the other two drugs. Overall, the results of this trial showed that valproate has better efficacy than lamotrigine and is better tolerated than topiramate. Based on these results, the authors suggested that valproate should remain the drug of the first choice for many patients with generalized and unclassified epilepsies. However, the authors also cautioned the use of valproate in women of child-bearing age due to its known side effect of teratogenicity. Subsequently, National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network guidelines recommended valproate and lamotrigine as initial choice ASMs for patients with newly diagnosed generalized epilepsy.^[18,19] With the availability of levetiracetam, subsequent trials compared levetiracetam against valproate. The Keppra (Levetiracetam) versus Older Monotherapy in Epilepsy Trial was a randomized, unblinded, pragmatic trial designed to show the superiority of levetiracetam to carbamazepine in patients with focal epilepsy and valproate in patients with generalized epilepsy.^[20] In this trial, 1688 patients were randomized to levetiracetam ($n = 841$)

or standard ASMs ($n = 847$; valproate: 347; carbamazepine: 500). In this study, there was no significant difference between levetiracetam and standard ASMs for the primary outcome of time-to-treatment withdrawal. On the other hand, the time to first seizure, which indicates efficacy, was better with standard drugs. However, the trial did not achieve its estimated sample size and failed to show the superiority of levetiracetam over standard drugs. Recently, results from the SANAD II trial (Arm B; Generalized epilepsy) have shown that valproate is superior to levetiracetam in patients with generalized epilepsies.^[21] In the per-protocol analysis, valproate was found to be superior as compared to levetiracetam for 12-month remission. Valproate was also found to be superior for the outcome of time-to-treatment failure (HR 0.65, 95% CI 0.50–0.83) while the risk of treatment failure due to adverse effects did not differ between the two groups. The results of SANAD II provide evidence that valproate is equally well tolerated and is more effective than levetiracetam in the management of patients with IGEs. Overall, the data indicate that valproate is the most effective drug in patients with IGEs.

With the availability of perampanel, brivaracetam, and lacosamide, few studies have reported the efficacy of these drugs as add-on therapy in patients with IGEs who are not controlled with other drugs. In a double-blind study of 162 patients, perampanel was found to be superior to placebo in reducing the frequency of GTCS over a period of 14 weeks.^[22] Similarly, in a real-world open-label study of 149 patients with IGEs not controlled with initial therapy, the 1-year seizure freedom rate with perampanel was 59% while the retention rate was 83%.^[23] Similar results were obtained with brivaracetam in a study of 39 patients with IGEs not controlled with other drugs.^[24] In an open-label study of 49 patients with IGEs, lacosamide was well tolerated and did not lead to worsening of absence or myoclonic seizures.^[25] Overall data with these newer ASMs indicate their efficacy as add-on therapy in patients with IGEs and their potential of use in patients with resistant IGEs. However, these drugs have still not been established as initial monotherapy and further evidence of their effectiveness as compared to established drugs is awaited.

ASMs in childhood absence epilepsy

The only truly double-blind randomized controlled trial in patients with IGEs has studied the efficacy of valproate, lamotrigine, and ethosuximide in patients with CAE. In this study, 453 children with newly diagnosed CAE were randomly assigned to treatment with ethosuximide (156), lamotrigine (149), or valproate (148).^[26] At 16 weeks, the freedom-from-failure rate was similar for ethosuximide and valproate (53% and 58%) which was higher than lamotrigine (29%). Rates of adverse events leading to treatment discontinuation were similar in the three groups. However, valproate was associated with higher rates of attention deficit than ethosuximide (49% vs. 33%). A 12-month extension of the trial demonstrated that valproate was associated with higher rates of weight gain, drug discontinuation, and attention deficits.^[27] This indicates that ethosuximide should be considered as first choice for CAE when

a patient has absence seizures only.^[28] However, ethosuximide is not effective against other seizure types including GTCS and hence valproate should be the first choice drug in such patients with CAE and GTCS. Oxcarbazepine, carbamazepine, phenytoin, tiagabine, and vigabatrin may worsen absence seizures or cause absence status epilepticus and should be avoided in children with CAE [Table 2].^[11-13]

ASMs in juvenile absence epilepsy

Being less common as compared to other types of IGEs and with clinical features often overlapping with CAE or JME, there are no studies that evaluated the efficacy of ASMs in patients with isolated JAE. The majority of the trials have included patients with CAE and JAE within the broad group of IGEs. Few studies involving a small number of patients have shown the efficacy of levetiracetam for the control of absence seizures. A small randomized double-blind trial involving 59 patients with newly diagnosed CAE or JAE showed that the seizure freedom rate at two weeks was higher with levetiracetam than placebo (23.7% vs. 4.8%, respectively; $P = 0.08$).^[29] In an open-label extension of this trial, 17 of 59 (28%) patients remained seizure free with levetiracetam. Thirty-four patients became seizure free with other ASMs such as valproate ($n = 27$), ethosuximide ($n = 6$), and the combination of valproate and ethosuximide. This along with other observational studies has suggested a moderate efficacy of levetiracetam in the control of absence seizures.^[29,30] The majority of the patients with JAE have associated generalized seizures and hence ethosuximide is not a useful drug in this group of patients. A small study involving 13 patients with refractory JAE has reported the efficacy of zonisamide in controlling absence seizures. Of the 13 patients, 5 (38%) patients became seizure free while others had more than 50% reduction in the frequency of absence seizures.^[31]

ASMs in juvenile myoclonic epilepsy

Valproate was established as an effective drug in patients with JME through many observational studies from the early 1990s onward with a response rate varying from 50% to 80%.^[32,33] Subsequently few randomized trials have reported the efficacy of levetiracetam in patients with uncontrolled JME. In a 12-week randomized controlled trial involving 120 patients with previously uncontrolled JME, Noachtar and colleagues reported a better efficacy of levetiracetam as compared to placebo (58.3% vs. 23.3%).^[34] Subsequently, few observational studies have reported the efficacy of levetiracetam monotherapy in patients with newly diagnosed JME.^[35] Few small unblinded randomized trials and observational studies have also suggested the efficacy of topiramate and zonisamide in patients with JME.^[36,37] Phenobarbitone was shown to control seizures in 80% of patients with JME in the original descriptions of Janz.^[38] Few observational data from India also indicate the efficacy of clobazam in patients with JME.^[39]

IGEs in Women of Reproductive Age Group

The available data and the clinical experience indicate that valproate is the most effective drug in patients with

IGEs. However, data from the last 20 years have suggested significant problems associated with valproate use in women of child-bearing age. Valproate has been shown to have the highest teratogenic potential among all the ASMs from pregnancy registries across the world. The reported rates of major congenital malformation (MCM) with valproate monotherapy in three large prospective ASM pregnancy registries vary from 6.7% to 10.3%.^[40-43] Apart from the risk of malformations, valproate use during pregnancy is associated with lower IQ in exposed children and a higher risk of autism spectrum disorders and attention-deficit hyperactivity disorders.^[44-46] In the prospective “Neurodevelopmental Effects of Antiepileptic Drugs” study, the IQ of the children exposed to high-dose valproate was 8–11 points lower as compared to children exposed to other ASMs.^[44] A Cochrane review of 22 prospective cohort studies and six registries has confirmed the association of in-utero valproate exposure and poor neurodevelopmental outcomes of children.^[45] Apart from the teratogenic potential of valproate, its use has also been shown to be associated with the development of polycystic ovarian disease, weight gain, and hair loss.^[47,48] Based on the teratogenic potential of valproate, many regulatory authorities in the United Kingdom, France, and European Union have issued regulatory guidelines restricting valproate use in women of child-bearing age.^[49,50] These guidelines have advocated the insertion of a visible reminder of the risks on the outer packaging of valproate medicines, proper counseling to apprise the women of risks associated with valproate use, maintaining a record that patient has been properly counseled regarding the risks of valproate use during pregnancy, and advise to use proper contraception during valproate use. The French National Agency for the Safety of Medicines and Health Products has banned the use of valproate for the treatment of bipolar disorders in women of child-bearing age.^[51] The European Union has introduced a risk acknowledgment form for patients and prescribers to confirm that appropriate advice has been given and understood. Although there has been no express ban on the use of valproate for epilepsy in women, guidelines advise its use only when all the other suitable options have been exhausted and no other option is available.

With these data, valproate should be considered as the last option for young women with IGEs. However, the benefits of not using valproate need to be balanced against the probable risk of poor seizure control in certain women with IGEs. Seizure control during pregnancy is as important as the side effects of ASMs. Valproate is the most effective drug in patients with IGEs and many patients can be controlled only with valproate and no other drug. It has been shown that patients not responding to valproate do not respond to any other monotherapy while patients with no response to other ASMs can be controlled with valproate.^[16,52] Stopping valproate or switching from valproate to other ASMs before or during pregnancy has been shown to worsen seizure control.^[53,54] Patients with higher seizure frequency during pregnancy have a higher risk of stillbirths, premature delivery, and low birth

weight babies.^[55,56] These data suggest that valproate cannot be completely banned in all women and it should be considered in selected patients who are not controlled with other ASMs after exercising all the precautions and discussing and documenting all the risks and benefits with the patients.^[57]

There is evidence to suggest that teratogenic and neurocognitive side effects of valproate are dose-dependent. Recent observations from the EURAP epilepsy and pregnancy registry showed that the rate of MCMs was 5.6% with dose <700 mg/day, 10.4% with a dose of 700 to <1500 mg/day, and 24.2% with dose ≥1500 mg/day.^[41] These rates were significantly higher compared to 2% MCM observed with lamotrigine <300 mg/day. Results from a pregnancy registry in South India also indicate a dose-dependent increased risk of MCM with valproate. Rates of MCM reported from the registry were 3.2% at doses ≤400 mg/day, 10.1% at doses between 400-800 mg/day, and 33.3% at doses higher than 800 mg/day.^[58] There is also growing evidence that valproate has a synergistic effect with lamotrigine and low-dose valproate combined with lamotrigine may be an option in selected patients with drug-resistant IGEs.^[59]

With the above discussion, certain conclusions can be drawn for the use of valproate in women of reproductive age group. Valproate should be initiated in women of the reproductive age group when other suitable options have been fully explored. The dose of valproate should be kept at the minimum possible and ideally less than 600 mg/day. If required, low-dose valproate can be combined with lamotrigine for a synergistic effect. All such patients should be properly counseled regarding contraception and the risks of valproate use during pregnancy. This should be documented in the risk acknowledgment form and proper informed consent should be obtained. It should be discussed with the patients during follow-up visits at least once a year and documented. If a woman with epilepsy receiving valproate conceives, she should be seen promptly to discuss the treatment options and outcomes. These women should be followed up regularly during pregnancy in close association with an obstetrician.

PROBLEMS WITH ASMs OTHER THAN VALPROATE

No ASM is ideal and all are associated with some or the other problems. Hence, the choice of the initial ASM should be individualized depending upon the patient characteristics. Levetiracetam is associated with behavioral issues such as anxiety, depression, and psychotic symptoms in 10–20% of the patients.^[60] Hence, levetiracetam should be avoided in patients with preexisting affective or psychotic symptoms. Topiramate and zonisamide can cause significant cognitive adverse effects and are usually avoided as initial monotherapy.^[61,62] However, both these drugs can cause weight reduction and can be considered as a good initial choice in overweight or obese individuals. Lamotrigine is relatively free of cognitive side effects but can lead to an allergic reaction in 2–5% of patients which necessitates very slow titration. Second, blood levels of lamotrigine fall significantly during the second trimester of pregnancy necessitating monitoring of serum lamotrigine

levels and increasing the dose of lamotrigine during the second trimester.^[63] Brivaracetam and perampamil are newer broad-spectrum ASMs with the potential of good efficacy in patients with IGEs.^[23-24] Brivaracetam is believed to have a lower incidence of behavioral side effects as compared to levetiracetam.^[64] Hence, these drugs may be considered as an option in patients with resistance to other ASMs. However, their safety in pregnancy has not been studied. More studies and clinical experience are required before recommending them for routine use in patients with IGEs.

TREATMENT RESISTANT IGEs

Drug-resistant epilepsy (DRE) is defined as the failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.^[65] In patients with IGEs, drug resistant has also been defined even with the failure of adequate doses of valproate to achieve seizure freedom.^[66,67] Approximately, 20–30% of the patients with IGEs have drug resistance. In JME, patients with all three seizure types (myoclonus, absences, and GTCS), associated behavior problems, and with EEG showing trains of polyspikes are more likely to have drug resistance.^[66]

Valproate remains the most effective drug in patients with IGEs and it has been shown that patients who do not respond to valproate monotherapy also do not respond to any other ASM.^[16,52] Hence, investigators have suggested that valproate resistance may be considered as a biomarker of drug resistance in IGEs. Various drugs have been found to be effective in patients with drug-resistant IGEs when compared with placebo.^[67] Valproate, being the most effective drug, should be tried in all patients who have failed to respond to other ASMs. In patients who do not respond to valproate, the only effective combination is valproate with lamotrigine and this combination should be tried in all the patients with difficult to control IGEs.^[59] Chances of seizure freedom in patients not responding to a combination of valproate and lamotrigine are remote. Few small series have demonstrated the efficacy of vagus nerve stimulation as palliative therapy in selected patients with drug-resistant IGEs.^[68] However, this palliative procedure should be considered in selected patients where all drug trials have been exhausted.

DURATION OF THERAPY IN IGEs

All types of IGEs with the notable exception of CAE are considered long-term disorders and require lifelong therapy. Long-term remission occurs in 65–80% of patients with CAE and ASM withdrawal can be attempted in these patients after 2–3 years of seizure freedom.^[3,69] Previous studies have reported that almost 100% of patients with JAE or JME recur on ASM withdrawal.^[70] Based on these observations, it is believed that these patients require lifelong treatment. However, in these studies, ASM withdrawal was attempted after 3–4 years of seizure freedom and at a younger age.

Table 4: Choice of ASMs according to the epilepsy syndrome

Epilepsy syndrome	First-line ASM	Second-line ASM	Resistant IGEs
Childhood absence epilepsy	Ethosuximide*	Valproate Lamotrigine	Ethosuximide + valproate; valproate + lamotrigine
JAE, JME, Epilepsy with GTCS alone	Valproate	Lamotrigine Levetiracetam Topiramate Zonisamide Clobazam, Perampanel	Valproate + lamotrigine
IGE in women of child-bearing age	Lamotrigine, Levetiracetam	Topiramate, Zonisamide	Low-dose valproate + lamotrigine

ASM: Antiseizure medicine; IGE: idiopathic generalized epilepsy; GTCS: generalized tonic-clonic seizure; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy. *Of all IGE syndromes, only ethosuximide has class I evidence for use in childhood absence epilepsy

Table 5: Choice of ASMs based on comorbidities and side benefits of medicines

Comorbidity	Preferred ASM	Drug (s) to be avoided
Obesity	Topiramate Zonisamide	Valproate
Depression	Lamotrigine Valproate	Levetiracetam
Cognitive dysfunction	Lamotrigine Levetiracetam	Topiramate Zonisamide Valproate
Migraine	Valproate Topiramate Lamotrigine	NA
Neuropathic pain	Lamotrigine	NA

ASM: Antiseizure medicine

Recent long-term studies in patients with JME with follow-up durations ranging from 30 to 45 years have shown that ASM can be withdrawn in one-third of patients.^[71] ASM withdrawal can be attempted in patients who are older than 40 years, are seizure-free for a minimum of five years, and have normal EEG. Prognosis in patients with GTCA is variable and has not been well studied. Practically, ASM withdrawal can be tried in these patients after 5 years of seizure freedom with a normal EEG.

TREATMENT APPROACH AND RECOMMENDATIONS

For practical purposes, the choice of first monotherapy in patients with IGEs is limited to valproate, lamotrigine, and levetiracetam. The above discussion outlines that valproate is the most effective ASM for the control of seizures in patients with IGEs and should remain the drug of the first choice except in certain special situations and populations. However, both lamotrigine and levetiracetam which have lower efficacy than valproate can be equally good options as initial monotherapy in patients with IGEs [Table 4]. In patients with CAE and absence seizures alone, ethosuximide, which has recently become available in India, should be the drug of the first choice because of its excellent efficacy and low potential for side effects. In women of child-bearing age, all the other options especially lamotrigine and levetiracetam should be explored

before switching over to valproate. Patients not responding to either lamotrigine or levetiracetam are unlikely to respond to other medicines and should be initiated on valproate. Patients with IGEs usually require low-to-moderate doses of ASMs and in our experience patients not responding to moderate doses are unlikely to respond to higher doses. In India, phenobarbitone may be a good cost-effective alternative in women of child-bearing age who are not able to afford newer ASMs. Zonisamide, topiramate, perampanel, and clobazam are alternative medicines that can be used in selected patients and patients not responding to a combination of valproate and lamotrigine. Various comorbidities in a given patient should be considered before choosing an ASM in the given patient [Table 5].

FUTURE PERSPECTIVE

As the evidence stands today, valproate is the most effective drug for the control of seizures in patients with IGEs. However, due to its adverse effect profile especially in women of child-bearing age, there is an urgent need for drugs with efficacy better or similar to valproate. Perampanel is a potential new broad-spectrum ASM that needs to be tested as monotherapy in patients with IGEs. In addition, we need to study the efficacy of various drug combinations in patients with IGEs which is a potential area of future research. Lastly, we need to study and discover clinical and genetic biomarkers for predicting the response to various ASMs in individual patients and to identify drug resistant in IGEs.

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