ANTIEPILEPTIC DRUG THERAPY: ROLE OF NEWER AGENTS

Imran I Ali

Department of Neurology, University of Toledo College of Medicine, Toledo, Ohio, United States

Correpondence to: Dr. Ali, Professor of Neurology, University of Toledo College of Medicine, 3000 Arlington Avenue, MS 1195, Toledo, Ohio 43614, USA
Email: imran.ali@utoledo.edu

Pak J Neurol Sci 2007; 2(4): 223-29

Epilepsy is a common neurological disorder with an estimated worldwide prevalence of approximately 1%. It is also a chronic, at times debilitating illness and carries with it an increased incidence of accidental injuries, psychiatric diseases as well as sudden death.[1] Early recognition and treatment is therefore of critical importance in reducing morbidity and mortality associated with the disease.

Appropriate antiepileptic therapy effectively controls seizures in approximately 60-75% of cases, either as monotherapy or as combination therapy.[2,3] Treatment of epilepsy is also important in improving the quality of life in patients with epilepsy and is frequently effective in treating co-existing disorders such as bipolar disease, neuropathic pain and migraine.[4]

Prior to 1990, only a handful of antiepileptic drugs (AEDs) were available for the treatment of epilepsy. These included phenytoin, carbamazepine, phenobarbital, primidone, and divalproex sodium, also known as the "older" antiepileptic agents. A number of agents have been approved by the Food and Drug Administration in the United States (and elsewhere in the world) since 1990 and are referred to as the "new AEDs" (Table 1). Interestingly, a number of these new agents (such as gabapentin and tiagabine) have shown limited utility or have been associated with serious adverse effects (vigabatrin and felbamate).[5] Brief information regarding dosing and adverse effects of these new AEDs is listed in Tables 2 and 3, respectively.

TABLE 1
New Antiepileptic Drugs

Felbamate
Gabapentin
Lamotrigine
Levetiracetam
Pregabalin
Tiagabine
Topiramate
Zonisamide

This review aims to focus on the currently utilized AEDs with demonstrable efficacy and tolerability and will summarize the current approach to medical management of epilepsy.

FELBAMATE

Felbamate was one of the first newer generation AEDs approved in the USA. The mechanism of action is related to NMDA antagonism, modulation of GABA and glycine receptors, as well as inhibition of sodium channels. It is effective in the treatment of partial seizures as well as Lennox-Gastaut Syndrome (LGS), a refractory form of secondary generalized epilepsy.[6,7] In a study of LGS with felbamate, there was a substantial decline in the frequency of atonic and tonic-clonic seizures.[6] Similarly, patients with partial epilepsy had a statistically significant decline in the number of seizures compared with placebo.[7]

However, within a few years of felbamate's approval, fatal aplastic anemia as well as hepatic failure were reported at a greater than expected rate. Although FDA did not pull it off the market, its use is now limited to the extremely refractory cases of epilepsy that are not amenable to surgical therapy and remain unresponsive to all other available agents. Patients requiring treatment with felbamate need to be informed of the potential risks of these fatal complications. The reported risk of hepatic failure with felbamate is 1 in 26-30,000, while the risk of aplastic anemia is 27-209 cases per million. Most of these complications occurred in the first year of treatment with felbamate; therefore, greater vigilance is required during this period.

It is recommended that a complete blood count and liver function profile be obtained frequently during the first year and periodically afterwards. There is no evidence that this monitoring alone will pick up development of felbamate-induced toxicity in the absence of good clinical oversight.

TABLE 2
Dosages of the new antiepileptic drugs

Antiepileptic drug	Initial dose	Maintenance daily dose	
Felbamate	300 mg bid (adults) 15 mg/kg/day (pediatrics)	2400-3600 mg 45 mg/kg/day	Two or three divided doses
Gabapentin	300 mg tid (adults) 10-15 mg/kg (pediatrics)	900-3600 mg (adults) 25-60 mg/kg (pediatrics)	Three divided doses
Levetiracetam	500 mg bid (adults) 10-20 mg/kg/day (pediatrics)	1000-3000 mg 60 mg/kg/day IV formulation available (same dose as oral)	Two divided doses
Topiramate	25 mg bid (adults) 1-3 mg/kg/day (pediatrics)	100-400 mg (adults) 5-9 mg/kg/day (pediatrics)	Two divided doses
Lamotrigine*	25 mg bid with EI^ AED, 25 mg qod with VPA (adults) 0.6 mg/kg/day with EI AED, 0.1 mg/kg/day with VPA# (pediatrics)	200-600 mg with EI AED, 100-300 mg with VPA (adults) 5-15 mg/kg/day with EI AED, 1-5 mg/kg/day with VPA (pediatrics)	
Zonisamide	100 mg qd (adult) 2-4 mg/kg (pediatrics)	200-600 mg (adults) 4-8 mg/kg (pediatrics)	Single daily dose
Oxcarbazepine	300 mg bid (adult) 8-10 mg/kg (pediatrics)	1200-2400 mg (adults) 20-50 mg/kg	Two divided doses
Tiagabine	4 mg/day (adult) Pediatric dosing not established	32-64 mg	Three to four divided doses
Pregabalin	25-50 mg bid or tid	200-300 mg	Two to three divided doses

*Consult prescribing guidelines for detailed information including use with "neutral" (non-enzyme inducing or inhibiting) AEDs. ^EI - enzyme-inducing.
#VPA - valproic acid.

GABAPENTIN

Gabapentin is a novel AED which was developed as a GABA agonist but at present this is not considered its primary mechanism of action. Recently, an inhibitory effect on the _2 _ receptor subunit of the calcium channel has been shown and postulated to be responsible for its antiepileptic effect.[8] Gabapentin is approved for the treatment of partial seizures only and may exacerbate absence seizures. This drug differs from other AEDs as it is absorbed through an L-amino acid transporter and has almost linear pharmacokinetics. It is renally excreted and the dose needs to be adjusted in patients with renal insufficiency.

Post-marketing experience suggests that gabapentin is well tolerated at lower doses but seems to have lesser efficacy than some of the other newer generation AEDs. It is on some occasions used as monotherapy in elderly patients with infrequent seizures as well as those with complex medical illnesses, as it lacks drug-drug interactions and systemic side effects. Although considered not to have major side effects, some patients do develop dizziness, somnolence, weight gain and peripheral edema.

LAMOTRIGINE

Lamotrigine is a well established AED with proven efficacy in partial as well as generalized epilepsy.[9] Lamotrigine acts by use- and voltage-dependant blockade of neuronal voltage-activated sodium channel, like phenytoin and carbamazepine. It is perhaps the most well studied of the newer agents, showing efficacy in partial and generalized epilepsy, both in children and adults.[10,11] Lamotrigine is also approved by the FDA for use as monotherapy in patients with partial seizures. It is effective in the treatment of Idiopathic Generalized Epilepsy (IGE) syndromes such as absence and juvenile myoclonic

TABLE 3
Adverse effects of the new antiepileptic drugs

Antiepileptic drug	Common adverse effects	Serious adverse effects
Felbamate	Insomnia, nausea, weight loss	Hepatic failure, aplastic anemia
Gabapentin	Dizziness, weight gain, fatigue, peripheral edema	None reported
Levetiracetam	Dizziness, fatigue, confusion, somnolence	Irritability, psychosis
Topiramate	Lethargy, dysphasia, confusion, distal paresthesiae, weight loss	Renal stones, glaucoma (rare)
Lamotrigine	Insomnia, restlessness, headaches, diplopia	Rash leading to SJS
Zonisamide	Somnolence, dizziness, anorexia, weight loss	Rash, renal stones, blood dyscrasias, hepatotoxicity
Oxcarbazepine	Sedation, dizziness, nausea, diplopia	Hyponatremia, rash, hepatotoxicity
Tiagabine	Sedation, impaired cognition	Rare cases of status epilepticus
Pregabalin	Sedation, weight gain, dizziness, thrombocytopenia, diplopia	Renal tumors in certain animals, edema

epilepsy (JME), but rare cases of exacerbation of myoclonus in progressive myoclonic epilepsy (PME) have also been reported.[12] Patients with PME treated with lamotrigine should be carefully observed for exacerbation of myoclonus.

In our experience as well, lamotrigine is effective as a broad spectrum drug and can be used in both partial onset and generalized epilepsies. Positive mood effects, lack of significant central nervous system side effects and reasonable safety profile makes it an attractive option as a first-line agent for most patients with epilepsy.[13,14] There are, however, some issues of clinical significance associated with this drug. There is an increased incidence of rash sometimes seen with rapid titration that does not follow the recommended guidelines. The rash may rarely lead to development of Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN). Fortunately, the incidence of rash (5-10%) has decreased since the dosing guidelines have been modified and the incidence of SJS/TEN is now reported to be less than 1% in most studies.[15]

Lamotrigine undergoes metabolic breakdown in the liver and is inhibited by divalproex sodium and sertraline. Lamotrigine levels are lowered by concomitant use of phenytoin, carbamazepine, and Phenobarbital, as well as estrogen-containing contraceptives. Since lamotrigine levels are lowered significantly by estrogens, it has the potential to lead to breakthrough seizures. Lamotrigine dosages may need to be increased in patients during the "estrogen" phase and lowered afterwards to avoid toxicity. Lamotrigine itself has negligible effects on serum levels of most medications. A 30 % reduction in estrogen levels of oral contraceptives has been noted but at present there are no reports of contraceptive failure with this agent (Table 4).[16]

TABLE 4
New antiepileptic drugs affecting oral contraceptives

Oxcarbazepine
Topiramate (dose 200 mg/day or >)
Lamotrigine (significance unknown)

One of the most important advantages of lamotrigine is related to its low incidence of teratogenicity in women with epilepsy.[14,17] Current analysis of retrospective data suggests that the incidence of major malformations is approximately 2-3% at doses of 200 mg per day or less, which is similar to that of the control population. Some concerns have been raised recently regarding an increased incidence of cleft lip in off-springs of women taking lamotrigine. The number of cases is quite small so far, so no firm conclusions can be drawn at this time. However, prior to any categorical and definitive conclusions regarding its safety in pregnancy can be made, it is recommended that patients should be informed of potential risks and benefits of therapy.

In summary, Lamotrigine appears to be a very effective AED in patients with new onset and refractory epilepsy in both pediatric and adult age groups, with limited adverse effects noted in randomized and controlled studies as well as based on post-marketing experience. Studies have also shown efficacy and remarkable tolerability in elderly patients with epilepsy.[18] Lamotrigine is also effective for treatment of bipolar disorder and the mood-stabilizing effects are sometimes evident in patients being treated for epilepsy with this agent.

LEVETIRACETAM

Levetiracetam is a truly novel antiepileptic because it binds to a hitherto previously unknown target for AEDs. Studies have shown its antiepileptic effects are related to binding of a synaptic vesicle protein SV2A.[19] Levetiracetam does not undergo extensive metabolism in the body and is renally excreted, so the dose may need to be adjusted in renal failure. It is an effective adjunctive treatment option for patients with partial epilepsy.[20] Recent studies have shown efficacy in idiopathic generalized epilepsy with and without myoclonus as well.[21] Since an intravenous formulation was introduced, there have been case reports of its role in hospitalized patients with seizures as well as for patients with acute repetitive seizures. As yet, no evidence has been found to suggest a role in early treatment of status epilepticus; however, anecdotal reports have suggested possible benefits in myoclonus associated with hypoxic-ischemic encephalopathy as well as in the treatment of non-convulsive status epilepticus.

Due to lack of any drug interactions and significant systemic side effects, levetiracetam is useful in patients with complex medical problems, as well as those requiring rapid titration of an AED. Intravenous loading with 1000-2000 mg usually does not produce any significant respiratory suppression, which is a distinct advantage in a patient with frequent seizures. In approximately 10-20% of patients treated with levetiracetam, somnolence, irritability, behavioral changes as well as marked exacerbation of underlying psychiatric disease has been noted.[23] In our experience, this does not appear to be a dose-related phenomenon and occurs early during treatment. Overall, this drug appears to be an effective agent for both partial and generalized epilepsy with limited drug interactions and favorable pharmacokinetics.

OXCARBAZEPINE

Oxcarbazepine was developed as an agent with a profile similar to carbamazepine. Due to absence of the epoxide metabolite, it was assumed that oxcarbazepine would have fewer adverse effects. However, oxcarbazepine has its own set of issues and has not replaced carbamazepine as a primary agent for the treatment of partial seizures.

Oxcarbazepine has a similar mechanism of action to carbamazepine, although unlike carbamazepine, it appears to have some inhibitory effects on potassium and calcium channels as well. Oxcarbazepine is approved for treatment of partial seizures in pediatric and adult age groups. It is an effective antiepileptic drug as monotherapy as well as adjunctive therapy for partial seizures. Although there are pharmacological similarities to carbamazepine, it is effective even in patients who have failed carbamazepine. Most of the evidence suggests that it is a significantly different drug compared with carbamazepine - based on efficacy, adverse effects, safety and tolerability. Interestingly, the side effects in our experience appear to be at par or at times greater than with carbamazepine. Hyponatremia is a particularly frequent problem; it is extremely uncommon in children but the risk increases with age and almost a third of patients above the age of 65 may develop this complication.[25] Other common side effects including rash, dizziness, diplopia, fatigue, as well as weight gain.

Oxcarbazepine also induces estrogen metabolism and may lead to oral contraceptive failure. Teratogenicity data at present shows conflicting results and the number of patients on monotherapy who have been pregnant has not reached statistical significance for any conclusions to be drawn at this time.

PREGABALIN

Pregabalin is a recent addition to the list of AEDs available for treatment of epilepsy. Like gabapentin, it binds to the alpha2-delta subunit of the calcium channel, modulating use-dependant neuronal activity. Pregabalin is effective for treatment of partial epilepsy as an adjunctive agent and has also been shown to be effective in treatment of diabetic neuropathy and post-herpetic neuralgia.[26] Pregabalin has anxiolytic properties that make it an attractive option in approximately 3-10% of patients with epilepsy who may have an underlying anxiety disorder or anxiety secondary to their epilepsy.

Robust efficacy data in partial epilepsy is somewhat tempered by an increased incidence of side effects that appear to be dose-related. These include dizziness, confusion, ataxia and somnolence. Substantial weight gain has also been seen in patients with increasing dose. Rare cases of hypersensitivity including idiosyncratic laryngeal swelling have been noted as well.

TIAGABINE

Tiagabine is a selective GABA reuptake blocker and is useful as an adjunctive agent in the treatment of partial epilepsy. It has limited use due to multiple daily, dosing requirements, significant CNS adverse events including exacerbation of depression, and behavioral problems as well as rare cases of development of non-convulsive status epilepticus.[27] Tiagabine remains an option for patients with refractory epilepsy and those with poor response to other first or second line AEDs.

TOPIRAMATE

Topiramate is also a broad spectrum AED with multiple mechanisms of action including inhibitory effects on sodium and calcium channels as well as the kainate subgroup of glutamate receptors. Additionally, it potentiates effects on GABA receptors as well as on the potassium channel. It is also a partial carbonic anhydrase inhibitor, although this effect is weak and probably of little consequence in relation to its efficacy but appears to be associated with some of the known side effects such as paresthesias, metabolic acidosis and urolithiasis. There is excellent efficacy data regarding topiramate in partial epilepsy in children and adults, as monotherapy as well as adjunctive therapy.[28] A number of studies have also shown statistically significant reduction in seizures in idiopathic generalized epilepsy.[29]

Topiramate has also been shown to be effective in prevention of migraine headaches.[29] Major side effects include cognitive impairment, weight loss, urolithiasis as well as somnolence. Some of these effects may be dose-related and more likely to occur above 200 mg per day. Reduction in oral contraceptive efficacy is noted at this dose as well.

ZONISAMIDE

Zonisamide is structurally related to other sulfa derivatives and functionally shares some of the features associated with topiramate. It has an inhibitory effect on both sodium and calcium channels. It is effective in treatment of partial epilepsy but efficacy has also been shown in some forms of generalized epilepsy such as JME and PME.[30-32] Zonisamide is effective as adjunctive therapy in patients with partial epilepsy and is also used as a second or third line alternative in refractory generalized epilepsy. Side effects include a hypersensitivity rash, somnolence, irritability, mood disorder and renal stones. Like topiramate, it is a weak carbonic anhydrase inhibitor and may lead to anhydrosis and possibly heat shock. Due to its presumed effects on dopaminergic pathways, there has been some interest in treating Parkinson's disease with zonisamide as well.[33]

SELECTING AN APPROPRIATE ANTIEPILEPTIC DRUG

The presence of additional AEDs has certainly given physicians a variety of different options for treatment of new and established patients with epilepsy. This availability of additional agents has not necessarily had a significant impact on the number of patients rendered seizure free. However, what it has allowed one to do is match a specific drug to a specific patient. Patients with epilepsy and their health care providers now have an option to choose an appropriate AED based on the spectrum of activity, side effect profile as well as efficacy in other concomitant disease states. Therefore, important issues to consider while selecting a specific AED are not only the type of epilepsy but also associated comorbidities, side effect profile, cost, and probability of compliance. As an example, a young obese man with new onset partial seizures and migraine headaches may benefit more from topiramate as monotherapy rather than carbamazepine. Topiramate in this case may also result in reduction in frequency of headaches and weight loss may be a welcome side effect.

APPROACH TO A PATIENT WITH PARTIAL EPILEPSY

In a patient diagnosed with partial epilepsy the choice of AED may vary based on a number of factors elucidated above. In young adults, lamotrigine is an excellent option both as initial and adjunctive therapy as it has minimal cognitive side effects and is extremely well tolerated by most patients. Lack of significant teratogenicity makes it a reasonable first choice in women of child bearing age. Additionally oxcarbazepine and topiramate are other agents that can be used as first line or as adjunctive therapy for partial epilepsy. Levetiracetam and pregabalin are reasonable alternatives as adjunctive therapy. In our experience, levetiracetam is a better adjunctive therapy option in some patients as it has no significant drug-drug interactions and is well tolerated in most cases. Approximately 15-20% of patients may develop behavioral problems and the drug should be discontinued in those patients. It can be used as monotherapy in some patients as well. Pregabalin has added advantage of being effective for treatment of neuropathic pain but side effects may limit its use in some patients. Zonisamide is an option for patients with both partial and generalized epilepsy. Tiagabine use is limited to third or fourth line in patients with partial epilepsy for the reasons discussed above. Felbamate is clearly reserved for patients with refractory

epilepsy who have not responded to other AEDs and are not considered appropriate surgical candidates. The benefits in these cases need to far outweigh the risks.

A sizable number of newly diagnosed cases of seizures are now in the elderly population that is inherently more susceptible to adverse cognitive effects of AEDs and may be more likely to be harmed by drugs with significant pharmacokinetic interactions. There have been a number of studies comparing carbamazepine, gabapentin and lamotrigine in the elderly, all of them suggest equal efficacy but greater tolerability with lamotrigine, a result that is not too surprising based on our experience and that of others.[18]

APPROACH TO A PATIENT WITH GENERALIZED EPILEPSY

In a patient with idiopathic generalized epilepsy divalproex sodium remains the drug of choice. Due to considerable side effects with this drug including weight gain, hepatotoxicity, thrombocytopenia, osteomalacia and tremors, alternative agents are frequently required. Data from randomized, controlled trials have shown that lamotrigine and topiramate are reasonable alternatives in patients with absence, myoclonic as well as generalized tonic-clonic seizures. A recent study has shown that levetiracetam reduces frequency of generalized and myoclonic seizures in IGE as well.[21] Zonisamide is an additional option for this type of epilepsy.

In patients with secondary generalized epilepsy, such as LGS, randomized, controlled trials have shown that topiramate, lamotrigine and felbamate are also effective as adjunctive therapy and considerable date supports their use in this type of epilepsy.

It should be noted that drugs such as gabapentin, tiagabine and oxcarbazepine may exacerbate seizures in generalized epilepsies and should be avoided.

ANTIEPILEPTIC AGENTS IN DEVELOPMENT

A number of novel AEDs are in different phases of development.[34] Brivaracetam is a structural analogue of levetiracetam; preliminary data suggests that is more potent and effective in treatment of both partial and generalized epilepsy with minimal tolerability issues. Another new AED currently in review by FDA for approval is lacosamide. Early data from randomized controlled trials would suggest robust efficacy in partial seizures. An added benefit appears to be availability of an intravenous formulation as well as efficacy in treatment of neuropathic pain. Rufinamide is also currently in Phase III trials for treatment of partial seizures. It has been shown to have significant efficacy in patients with LGS; however the present data shows only modest benefits in partial epilepsy. Retigabine is a novel AED which activates a specific type of potassium channel (KCNQ2/3). In two randomized clinical trials it has demonstrated dose-related efficacy for treatment of partial seizures as an adjunctive agent. Numerous other agents are also currently in development and the reader is referred to a recent review for more detailed information.[34]

SUMMARY

There are currently multiple new AEDs available for treatment of epilepsy. Their role in treatment of individual patients requires a thorough understanding of the pharmacological characteristics of these agents as well as that of the underlying epilepsy syndrome. Careful matching of the drug to the patient may not only control epilepsy but may also improve the quality of life of that individual, which should be the ultimate goal.

REFERENCES

1. Johnston A, Smith P. Sudden unexpected death in epilepsy. *Expert Rev Neurother* 2007; **7**(12):1751-61.
2. French JA, Kanner AM, Bautista J, et al. Treatment of new-onset epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2004;**45**(5):401-9.
3. French JA, Kanner AM, Bautista J, et al. Treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2004;**45**(5):410-23.
4. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 2008;**22**(1):27-47.
5. Wong IC, Lhatoo SD. Adverse reactions to new anticonvulsant drugs. *CNS Drugs* 2000;**23**(1):35-56.
6. The Felbamate Study Group in Lennox-Gastuat Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastuat syndrome). *N Engl J Med* 1993;**328**(1):29-33.
7. Bourgeois BF. Felbamate in the treatment of partial-onset seizures. *Epilepsia* 1994;35 *Suppl* **5**:S58-61.
8. Gilron I. Gabapentin and pregabalin for chronic

neuropathic and early postsurgical pain: current evidence and future directions. *Curr Opin Anaesthesiol* 2007;**20**(5):456-72.
9. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;**369**(9566):1016-26.
10. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblended randomised controlled trial. *Lancet* 2007; **24**;369(9566):1000-15.
11. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. *Epileptic Disord* 2007;**9**(4):353-412.
12. Crespel A, Genton P, Berramdane M, et al. Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 2005;**65**(5):762-4.
13. Malik S, Arif H, Hirsch LJ. Lamotrigine and its applications in the treatment of epilepsy and other neurological and psychiatric disorders. *Expert Rev Neurother* 2006;**6**(11):1609-27.
14. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. *Seizure*. 2007 (In press)
15. Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007;**68**(20):1701-9.
16. Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006;**61**(2):191-9.
17. Cunnington M, Ferber S, Quartey G, et al. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007;**48**(6):1207-10.
18. Saetre E, Perucca E, Isojärvi J, et al. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia* 2007;**48**(7):1292-302.
19. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci U S A.* 2004;**101**(26):9861-6.
20. Grant R, Shorvon SD. Efficacy and tolerability of 1000-4000 mg per day of levetiracetam as add-on therapy in patients with refractory epilepsy. *Epilepsy Res* 2000;**42**(2-3):89-95.
21. Noachtar S, Andermann E, Meyvisch P, et al. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology 2008;**70**(8):607-16.
22. Rüegg S, Naegelin Y, Hardmeier M, et al. Intravenous levetiracetam: Treatment experience with the first 50 critically ill patients. *Epilepsy Behav* 2008 (In press)
23. Mula M, Trimble MR, Sander JW. Psychiatric adverse events in patients with epilepsy and learning disabilities taking levetiracetam. *Seizure* 2004;**13**(1):55-7.
24. Martinez W, Ingenito A, Blakeslee M, et al. Efficacy, safety, and tolerability of oxcarbazepine monotherapy. *Epilepsy Behav* 2006;**9**(3):448-56.
25. Dong X, Leppik IE, White J, Rarick J. Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005;**65**(12):1976-8.
26. Lozsadi D, Hemming K, Marson A. Pregabalin add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev* 2008;**(1)**:CD005612.
27. Koepp MJ, Edwards M, Collins J, et al. Status epilepticus and tiagabine therapy revisited. *Epilepsia* 2005;**46**(10):1625-32.
28. Lyseng-Williamson KA, Yang LP. Spotlight on topiramate in epilepsy. *CNS Drugs* 2008;**22**(2):171-4.
29. Fontebasso M. Topiramate for migraine prophylaxis. *Expert Opin Pharmacother* 2007;**8**(16):2811-23.
30. Baulac M, Leppik IE. Efficacy and safety of adjunctive zonisamide therapy for refractory partial seizures. *Epilepsy Res* 2007;**75**(2-3):75-83.
31. Kyllerman M, Ben-Menachem E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. *Epilepsy Res* 1998;**29**(2):109-14.
32. O'Rourke D, Flynn C, White M, et al. Potential efficacy of zonisamide in refractory juvenile myoclonic epilepsy: retrospective evidence from an Irish compassionate-use case series. *Ir Med J.* 2007;**100**(4):431-3.
33. Miwa H. Zonisamide for the treatment of Parkinson's disease. *Expert Rev Neurother*. 2007;**7**(9):1077-83.
34. Bialer M, Johannessen SI, Kupferberg HJ, et al. Progress report on new antiepileptic drugs: a summary of the Eigth Eilat Conference (EILAT VIII). *Epilepsy Res* 2007;**73**(1):1-52.