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AN UPDATE ON ANTIEPILEPTIC AGENTS: FOCUS ON SECOND GENERATION TREATMENT OPTIONS

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Epilepsy is a neurological disorder characterized by sudden recurring attacks of motor, sensory, or psychic malfunction. This disorder affects approximately 2.3 million Americans.¹ Even though recent surgical advances in the treatment of epilepsy have been made, the primary form of treatment is still pharmacological.

Epilepsy has been viewed with a negative prognosis throughout history. Hippocrates held the belief that seizures beginning in adulthood lasted until death.² Gowers later said, "the spontaneous cessation of seizures is an event too rare to be anticipated in any given case."³ These negative views of epilepsy treatment were held for decades despite the emergence of the anticonvulsants, phenytoin and phenobarbital in the early 1900s. These medications were the first approved for the treatment of epilepsy by the FDA in 1939. The most recent FDA approval for epilepsy was pregabalin in 2005, which has been shown in combination with other antiepileptic drugs to reduce the frequency of seizures.⁴

The cost of epilepsy has a large impact on both the individual and society. The estimated annual cost of epilepsy in the U.S. is \$15.5 billion.⁵ The individual's quality of life is affected from both a physical and psychological standpoint. Kanner showed that 20%-55% of patients with uncontrolled epilepsy suffer from depression.⁶ Individuals with

this disorder must overcome limitations with independence, problems with work and education, and deal with the potential for social embarrassment.⁷ This article will discuss some of the advantages to choosing the newer second generation anticonvulsants when treating epilepsy.

TREATMENT OPTIONS: GENERAL OVERVIEW

Many of the recent advances in the pharmacological treatment of epilepsy have been due to our greater understanding of this disorder. The newer second-generation agents offer more advantages including improved safety and efficacy over first generation antiepileptic drugs (AEDs). Many of the newer AEDs have more predictable pharmacokinetics than the first generation AEDs. Most of the first generation AEDs are metabolized hepatically and are strong enzyme inducers of the cytochrome P450 system (phenytoin, carbamazepine, phenobarbital, and primidone). The second generation AEDs have less hepatic metabolism and cytochrome P450 induction, fewer drug interactions, and lower protein binding.⁸ However the newer AEDs are not more efficacious than the older generation AEDs (phenytoin, valproic acid and carbamazepine) when treating newly diagnosed partial or generalized seizures.^{9,10} While the second generation AEDs exhibit similar efficacy

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Table 1. Summary of First Generation Anticonvulsant Epileptic Drugs¹¹⁻¹⁴

Agent (year approved)	Proposed Mechanism of Action	Indications	PK (F,VD,T½)	Drug-Drug Interactions	Serious Side Effects	Typical Target Dose (mg/day)	Cost
Phenytoin (1939)	Modulates voltage-dependent sodium channels	Partial, generalized tonic-clonic, myoclonic seizures	70-100% 0.63L/kg 6-24 hrs	CYP enzyme inducer	Rash, pseudolymphoma, Stevens-Johnson syndrome, lupus-like syndrome	200-300, bid, tid	100mg (#100) = \$25.99
Phenobarbital (1939)	Promotes GABA responses, reduces glutamate effects	Partial, generalized tonic-clonic, myoclonic seizures	95% 0.55L/kg 53-118 hrs	Carbamazepine, Lamotrigine, Oxcarbazepine, Phenytoin, Tiagabine, Valproate	Cognition impaired, Stevens-Johnson syndrome, depression	50-200, daily, bid	64.8mg (#100) = \$12.99
Primidone (1954)	Promotes GABA responses, reduces glutamate effects	Partial, generalized tonic-clonic, myoclonic seizures	100% 0.64-0.86L/kg 5-18 hrs	CYP enzyme inducer	Cognition impaired, Stevens-Johnson syndrome, depression	500-750, tid	250mg (#90) = \$69.99
Ethosuximide (1960)	Modulates voltage-dependent T-type calcium channels	Absence and myoclonic seizures	93% 0.70L/kg 53 hrs	Phenytoin, Valproate, Carbamazepine	Gastrointestinal events, psychotic episodes, depression	1000-3600, bid	250mg (#30) = \$42.99
Carbamazepine (1968)	Blocks use-dependent sodium channels	Partial, generalized tonic-clonic, myoclonic seizures	85% 1.40L/kg 25-65 hrs	Lamotrigine, Tiagabine, Valproate	Rash, hyponatremia, Stevens-Johnson syndrome	600-1200, bid, tid	200mg (#60) = \$14.99
Valproate (1978)	Increases GABA brain concentrations	Partial, generalized tonic-clonic, absence and myoclonic seizures	100% 0.92-1.25L/kg 9-16 hrs	CYP enzyme inhibitor, Phenytoin	Hyperammonemia, pancreatitis, thrombocytopenia, Aplastic anemia	600-1500, bid slow release, tid	250mg (#30) = \$14.99

F, bioavailability; VD, volume of distribution; T½, half-life; bid, twice a day; tid, three times a day; PK, pharmacokinetic

when treating newly diagnosed epilepsy, the newer treatment options have a favorable response rate in a number of refractory epilepsy cases. The side effects seen in first generation anticonvulsants are more severe compared to most second generation AEDs. Many of the older AEDs require close monitoring of serum levels and have black-box warnings to warn patients of these potentially life-threatening reactions.

FIRST GENERATION EPILEPSY TREATMENTS

Before 1993, the management of epilepsy was limited to six major AEDs. These were referred to as the older or traditional AEDs and consisted of Phenobarbital, Primidone, Phenytoin, Valproate, Carbamazepine and Ethosuximide. While all of the older AED's were efficacious, their long-term safety was questionable (see Table 1). Development of newer antiepileptic medications with few serious adverse effects, minimal drug interactions, and broader spectrums of activity was needed.

SECOND GENERATION EPILEPSY TREATMENTS

The current second generation antiepileptic drugs include Felbamate, Gabapentin, Lamotrigine, Topiramate, Tiagabine, Zonisamide, Levetiracetam, Oxcarbazepine and Pregabalin (see Table 2). For this review five of the newer AEDs (Lamotrigine, Oxcarbazepine, Topiramate, Pregabalin, and Tiagabine) were selected based on their spectrum of use and potential place in epilepsy treatment.

CLINICAL TRIAL DATA

Stephen et al. performed a randomized, prospective study to compare the efficacy and tolerability of sodium valproate (VPA) and lamotrigine (LTG) monotherapy.¹⁵ This study included 225 patients, median age 35 years, who were followed for 12 months. Twelve month seizure-free rates were identical (47%) in the VPA and LTG treatment arms. But 23% VPA versus 13% LTG withdrew due to adverse events. Brodie et al. compared LTG to carbamazepine (CBZ) for a 24 week period.¹⁶ They en-

Table 2. Summary of Second Generation Anticonvulsant Epileptic Drugs¹¹⁻¹⁴

Agent (Yr approved)	Proposed Mechanism of Action	Indications	PK (F,VD,T½)	Drug-Drug Interactions	Serious Side Effects	Typical Target Dose (mg/day)	Cost
Felbamate (1993)	Excitatory NMDA and inhibitory GABA brain mechanisms	Partial seizures and Lennox-Gastaut syndrome refractory to other AED	>90% 0.75L/kg 14-23 hrs	Carbamazepine, Phenytoin, Valproic Acid and Gabapentin	Aplastic anemia and hepatic failure	2400-3600, bid, tid	400mg (#90) = \$205.79
Gabapentin (1994)	Indirect effects on calcium channels and increase GABA	Adjunctive management of partial seizures	Dose dependent 0.9L/kg 5-9 hrs	Cimetidine and Antacids	None	900-2400, bid, tid	600mg (#90) = \$92.99
Lamotrigine (1995)	Inhibition of voltage-activated sodium channels	Partial, generalized tonic-clonic, absence and myoclonic seizures	98% 1.2L/kg 15-35 hrs	Carbamazepine, Phenytoin, Valproic Acid and Phenobarbital	Stevens-Johnson syndrome	100-400, daily, bid	25mg (#30) = \$89.99
Topiramate (1995)	Modulation of voltage-dependent sodium channels and GABA inhibition	Adjunctive treatment of partial seizures	81-95% 0.6-1L/kg 20-30 hrs	Carbamazepine, Phenytoin, Phenytoin, Primidone, Valproic Acid and Oral Contraceptives	Kidney stones, oligohydrosis, glaucoma	100-400, bid	100mg (#60) = \$369.87
Tiagabine (1996)	Blocks GABA reuptake increasing GABA concentrations	Adjunctive treatment with partial epilepsy	90-95% 1.4L/kg 5-8 hrs	Carbamazepine, Phenytoin, Primidone and Valproic Acid	Spike-wave stupor	36-60, tid	16mg (#30) = \$225.39
Zonisamide (1999)	Blocks voltage-sensitive sodium channels	Adjunctive treatment of partial onset seizures	40-60% 1.5L/kg 50-70 hrs	Carbamazepine, Phenytoin, Primidone and Valproic Acid	Kidney stones, oligohydrosis, rash	300 daily	50mg (#100) = \$91.99
Levetiracetam (1999)	Unknown mechanism	Adjunctive therapy for the management of partial seizures, myoclonic seizures	100% 0.5-0.7L/kg 6-8 hrs	Phenytoin	None	1000-3000, bid	1000mg (#60) = \$428.88
Oxcarbazepine (2000)	Blocks voltage-sensitive sodium channels	Partial seizures and generalized tonic-clonic seizures	95% 0.75L/kg 8-15 hrs	Phenytoin, Lamotrigine and Oral Contraceptives	Hyponatremia, rash	800-1800, bid, tid	600mg (#60) = \$259.98
Pregabalin (2005)	Indirect effects on calcium channels and increase GABA	Partial and secondary generalized tonic-clonic seizures	90% 0.56L/kg 5-7 hrs	Oxycodone, Lorazepam and Ethanol	None	150-600, daily	150mg (#30) = \$73.49

F, bioavailability; VD, volume of distribution; T½, half-life; bid, twice a day; tid, three times a day; PK, pharmacokinetic

rolled 150 elderly patients (>65 yrs) and found a greater percentage of LTG patients remained seizure free the last 16 weeks (LTG 39%, CBZ 21%, p = 0.027). The hazard ratio for withdrawal was 2.4 (95% CI 1.4-4.0) meaning that patients were more than twice as likely to withdraw from the CBZ treatment arm. Both of these trials showed similar efficacy and better tolerability of lamotrigine compared to first generation epilepsy treatments.

Schachter and colleagues conducted a double-blind, randomized, placebo-controlled, monotherapy trial for partial seizures comparing oxcarbazepine to

placebo.¹⁷ Oxcarbazepine 1,200mg was administered twice daily in hospitalized patients with refractory partial seizures for ten days. The results showed both the primary (time to meeting one of the exit criteria) and secondary (percentage of patients who met one of the exit criteria) efficacy variables were statistically significantly better for the oxcarbazepine arm (p= 0.0001). The total partial seizure frequency per 9 days was also significantly better for oxcarbazepine (p= 0.0001).

Bill and colleagues compared oxcarbazepine (OXC) versus phenytoin (PHT) in a double-blind,

randomized, parallel-group trial.¹⁸ The study used 287 patients randomized in a 1:1 ratio. No statistically significant difference was found in the efficacy analysis between the two treatment arms. The OXC arm had 3.5% of patients discontinue treatment early for tolerability issues versus 11% in the PHT group. This result showed a statistically significant difference in favor of OXC.

Privitera et al. completed a multinational, randomized, double-blind trial comparing topiramate (TPM), carbamazepine (CBZ), and valproate (VPA).¹⁹ They randomized 613 newly diagnosed epilepsy patients into two treatment arms. Treatment was with the traditional antiepileptic drugs (CBZ or VPA), TPM 100mg/day, or TPM 200mg/day. There was no difference among the treatment groups with regard to efficacy, but TPM 100mg/day was associated with the fewest discontinuations due to adverse events.

Krakov and colleagues conducted an open-label, observational prospective study assessing the effectiveness of topiramate (TPM) as add-on therapy.²⁰ The investigators enrolled 450 patients who had at least one seizure in the previous 12 weeks. The vast majority (95% of patients) were taking either CBZ or VPA and were followed for 1 year. During the 12 month study, a median of 2.8 seizures per month were recorded which was significantly reduced to 0.7 per month during the complete treatment phase ($p=0.0001$). Nearly three-fourths of these patients (72%) had greater than 50% seizure reduction and only 5% ended treatment early because of adverse effects.

Arroyo et al. performed an international, multicenter, 12-week, double-blind, randomized study comparing placebo, pregabalin (PGB) 150mg/day and 600mg/day as add-on treatment for patients with refractory partial seizures.²¹ This trial enrolled 287 patients and randomized them into three treatment arms. The primary efficacy was the reduction of seizures from baseline during the 12-week treatment. PGB 150mg/day and 600mg/day were significantly more effective than placebo in decreasing seizure rates ($p=0.0007$ and $p<0.0001$, respectively, vs. 0.9). Additionally, PGB 150mg/day and 600mg/day was efficacious and well tolerated when used as add-on therapy in patients with partial seizures.

Another randomized, double-blind, placebo-controlled study evaluating flexible-dose and fixed-dose pregabalin treatment was recently published by

Elger, et al.²² This trial randomized 341 patients to placebo, pregabalin 600mg/day BID fixed-dose arm and a pregabalin flexible-dose arm (150 and 300mg/day for 2 weeks each; 450 and 600mg/day for 4 weeks each, BID). Both PGB arms decreased seizure frequency, by 35.4% in the flexible-dose arm ($p=0.0091$) and 49.3% in the fixed-dose arm ($p=0.0001$), compared to 10.6% in the placebo arm ($p=0.0337$). The authors concluded PGB to be highly efficacious and well-tolerated in both the fixed and flexible-dose arms compared to placebo.

Kalviainen et al. performed a multicenter, double-blind, parallel-group, placebo-controlled trial comparing the efficacy and tolerability of tiagabine and placebo in refractory partial seizures.²³ Patients ($n=154$) were randomized to either a tiagabine or placebo treatment arm during the 12 week study. There was a significant reduction in the median 4-week seizure rate for all partial seizures and simple partial seizures ($p < 0.05$). Tiagabine was generally well-tolerated, with most adverse effects being mild to moderate. This study showed tiagabine dosed lower than what is normally accepted (10mg TID), is well tolerated and has efficacy for treatment of refractory partial seizures.

Dodrill et al. evaluated the differences between tiagabine (TGB), carbamazepine (CBZ) and phenytoin (PHT) when used as add-on therapy in uncontrolled partial seizures.²⁴ 277 patients were divided into two groups, one group currently receiving CBZ and the other PHT. These groups each contained two treatment arms, the CBZ baseline group received either TGB or PHT add-on treatment and the PHT baseline group received either CBZ or TGB treatment. The results from the baseline CBZ group revealed no differences in test scores between TGB and PHT. The results from the baseline PHT group showed patients in the TGB arm treatment had improved verbal fluency as well as quicker responses with motor speed tests compared to patients treated with CBZ. But TGB patients in the baseline PHT reported less positive mood and more financial concerns than the CBZ treatment arm. Overall, treatment with TGB showed very few differences when compared to CBZ and PHT as add-on treatment in uncontrolled partial seizures.

SUMMARY

Second generation AEDs may offer a favorable choice in treating epileptic seizures but they have not

Table 3. Overview of Clinical Trials Involving AED Treatments¹⁵⁻²⁴

Trial	Agent(s)	Comparator(s)	Design	Patient Characteristics	Results
Stephen et al. (2007)	Lamotrigine	Sodium Valproate	R, PS	N = 226 Mean age 35yr Age range 13-80	No difference in efficacy, but Lamotrigine was better tolerated (p= 0.046)
Brodie et al. (1999)	Lamotrigine	Carbamazepine	M, R, DB	N = 150 Mean age 77yr Age range >65	Seizure free last 16 weeks (LTG 39%, CBZ 21%, p= 0.027)
Schachter et al. (1999)	Oxcarbazepine	placebo	R, DB, PC	N = 102 Mean age 33yr Age range 11-62	All variables studied statistically favored Oxcarbazepine (p=0.0001)
Bill et al. (1997)	Oxcarbazepine	Phenytoin	R, DB, PG	N = 287 Mean age 27yr Age range (OXC) 16-63 Age range (PHT) 15-91	No difference in efficacy, but OXC showed significant better tolerability
Privitera et al. (2003)	Topiramate	Carbamazepine, Valproate	M, R, DB	N = 613 Mean age 29yr Age range 6-64,>65	Similar efficacy in all arms, TPM 100mg/day fewest adverse events
Krakov et al. (2007)	Carbamazepine w/ Topiramate and Valproate w/ Topiramate	Carbamazepine and Valproate	OL, O, P	N = 450 Mean age 40yr Age range 10-93	72% had > 50% seizure reduction, 5% discontinued treatment early
Arroyo et al. (2004)	Pregabalin	placebo	M, R, DB	N = 287 Mean age 37yr Age range 17-73	PGB was highly efficacious and well-tolerated v. placebo
Elger et al. (2005)	Pregabalin	placebo	R, DB, PC	N = 341 Mean age 41yr Age range 18-78	PGB was highly efficacious and well-tolerated v. placebo
Kalviainen et al. (1998)	Tiagabine	placebo	M, R, DB, PC	N = 154 Mean age 36yr Age range 16-75	Significant seizure reduction (p < 0.05), well-tolerated
Dodrill et al. (2000)	Carbamazepine w/ Tiagabine and Phenytoin w/ Tiagabine	Carbamazepine w/ Phenytoin and Phenytoin w/ Carbamazepine	R, DB	N = 277 Mean age 38yr Age range >16	Statistically no significant differences between treatment arms

R = randomized; PS = prospective study; M = multicenter; DB = double-blind; PC = placebo-controlled; PG = parallel-group; OL = open-label; O = observational

replaced the first generation AEDs. The newer drugs are as efficacious as the older ones with a trend toward fewer side effects. The few head-to-head trials between the older and newer AEDs makes the preferential selection of any agent difficult. Although the long term goal of seizure freedom remains a difficult task for many patients, a better understanding of the disease will hopefully move treatment from seizure suppression to prevention of epilepsy.

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