Comparative Pharmacological Studies of Newer Versus Older Antiepileptic Drugs

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ABSTRACT:

According to recent statistics, there are about 50 million epileptics across the globe. Antiepileptic drugs represent a primary method for epilepsy treatment, yet, in the last thirty years, more than twenty new antiepileptic drugs were developed, thus making it rather difficult to identify the right drug. This review comprehensively evaluates the difference between first-, second-, and third-generation AEDs in several aspects, including pharmacokinetics, pharmacodynamics, efficacy, side effects, tolerance, interaction, and usage in different patients.

Compared with older antiepileptic drugs, newer ones provide better linear pharmacokinetics, increased oral bioavailability (gabapentin is an exception), decreased plasma protein binding, and a lower likelihood for interaction with cytochrome P450 enzymes. Nonetheless, a number of comparative studies proves that older medications (phenytoin, carbamazepine, valproic acid, and phenobarbital) are no less effective in seizure prevention than their newer counterparts. The best choice for women of reproductive age is either levetiracetam or lamotrigine since the teratogenic effects (likelihood for major congenital malformations) of valproate is 9-11% while lamotrigine produces no more than 2-3%.**Keywords:** Antiepileptic drugs; epilepsy; pharmacokinetics; comparative efficacy; drug safety; newer AEDs; older AEDs.

1. Introduction

1.1 Overview of Epilepsy

Epilepsy is a neurological condition that is recurrent in nature and occurs due to unprovoked seizures as a result of abnormal or synchronous activity of neurons in the brain. As per International League Against Epilepsy (ILAE), epilepsy is categorized into three categories which include: at least two unprovoked seizures more than 24 hours apart, one unprovoked seizure with significant possibility of future occurrence, and epilepsy syndromes.

1.2 Burden and Epidemiology

There is a huge global burden associated with epilepsy. According to estimates by the World Health Organization (WHO), there are about 50 million individuals with epilepsy around the world, thus being among the most prevalent neurological disorders in the world. Important observations from the disease's epidemiology include:

Annual incidence: 50 to 120 per 100,000 population

- **Point prevalence:** 4 to 10 per 1,000 population
- **Lifetime prevalence:** 1.5% to 5% across different populations
- **Age distribution:** Bimodal peaks in childhood (<5 years) and elderly (>60 years)

The economic burden of epilepsy is immense. Each year in the United States, the financial burden of epilepsy is over $15 billion, taking into account direct costs (treatment, hospitalization), indirect costs (work disability, caregiving expenses), and psychosocial costs.

1.3 The Evolution of Antiepileptic Drug Therapy

The pharmacological management of epilepsy has undergone remarkable transformation:

1.4

Era	Years	Key Drugs
First-Generation	1912–1978	Phenobarbital (1912), Phenytoin (1938), Carbamazepine (1974), Valproic acid (1978), Ethosuximide (1960)
Second-Generation	1990–2009	Gabapentin, Lamotrigine, Topiramate, Levetiracetam, Oxcarbazepine, Zonisamide, Pregabalin
Third-Generation	2010–Present	Lacosamide, Perampanel, Brivaracetam, Cenobamate, Fenfluramine, Ganaxolone

Rationale for Comparative Studies

This literature review critically assesses several important questions relating to antiepileptic drugs (AEDs), including whether novel AEDs exhibit better efficacy than old drugs; whether their enhanced safety makes their increased cost justifiable; which AEDs exhibit the best safety profile; and which AEDs are preferred for special cases.

2. Methodology

2.1 Literature Search Strategy

A systematic literature review was done via PubMed, Scopus, Web of Science, and Cochrane library databases, looking for papers from 1990 to 2026 with key search words such as "antiepileptic drugs," "recent AEDs," "efficacy comparison," "pharmacokinetics," and "safety profile."

2.2 Inclusion and Exclusion Criteria

Studies were included if they were randomized controlled trials comparing antiepileptic drugs (AEDs), systematic reviews, meta-analyses, or real-world observational studies with more than 100 participants. Research evaluating the efficacy, safety, tolerability, or cost-effectiveness of newer and older AEDs was considered. Only full-text articles published in English were included. Studies focusing on special populations, such as children, older adults, and pregnant women, were also eligible. Exclusion criteria included case reports, case series, editorials, conference abstracts without sufficient data, non-English publications, animal studies, and studies with inadequate methodological quality or insufficient outcome data.**2.3 Quality Assessment**

Study quality was assessed using Cochrane Risk of Bias Tool for RCTs and Newcastle-Ottawa Scale for observational studies.

3. Pathophysiology of Epilepsy

3.1 Neuronal Hyperexcitability and Seizure Generation

Epilepsy refers to a disorder of the nervous system that entails recurrent seizures due to an excessive and synchronized activity of neurons in the brain. The essential pathophysiological factor in the formation of a seizure is an imbalance between excitatory and inhibitory neurotransmission in the central nervous system. An increase in the level of excitability can be achieved either by an increased glutamate neurotransmission or an overactivity of excitatory receptors such as NMDA and AMPA. On the contrary, an inadequate inhibition could be achieved as a result of an underactivity of GABA neurotransmitters, their receptors, or inhibitory interneurons. Other factors contributing to a higher excitability of neurons include physical trauma to the brain, gene mutations, infections, brain tumors, and other neurological disorders that affect the proper functioning of the neural circuitry and create an opportunity for developing abnormal synapses.**3.2 Role of Neurotransmitters**

Excitatory (Glutamate): Glutamate is the primary excitatory neurotransmitter in the central nervous system and is key in neuron communication and in the development of seizures. Glutamate acts via ionotropic receptors like AMPA, NMDA, and kainate receptors. The AMPA receptors function to promote fast excitatory synapses, while NMDA receptors play a role in slow excitatory responses and synaptic plasticity. Overactivation of these receptors, especially NMDA receptors, will lead to a rise in the amount of intracellular calcium and cause excitotoxicity. Excess secretion of glutamate during seizures causes depolarization of neurons and causes them to be hyperexcitable.

Inhibitory (GABA): GABA is an important inhibitory neurotransmitter in the brain that functions primarily by modulating chloride channels through the GABA receptors. Pharmacologically, several studies have compared that dysfunction in GABAergic inhibitions results in various epilepsy syndromes. Older and modern antiepileptics work by increasing GABA inhibition to minimize seizure disorders among epileptic patients.

3.3 Ion Channels

Voltage-gated ion channels regulate neuronal excitability:

Channel Type	Function	Epilepsy Relevance
Sodium channels	Action potential propagation	SCN1A mutations cause Dravet syndrome
Calcium channels	Burst firing, neurotransmitter release	T-type channel mutations linked to absence epilepsy
Potassium channels	Repolarization	KCNQ2/3 mutations cause benign familial neonatal epilepsy

4. Classification of Antiepileptic Drugs

4.1 Older (First-Generation) AEDs

Drug	Year	Primary Indication	Key Limitations
Phenobarbital	1912	GTCS, focal seizures	Sedation, cognitive impairment, dependence

Phenytoin	1938	Focal, GTCS	Nonlinear PK, narrow TI, gingival hyperplasia
Carbamazepine	1974	Focal, GTCS	Autoinduction, drug interactions, rash
Valproic acid	1978	Broad spectrum	Weight gain, hepatotoxicity, teratogenicity
Ethosuximide	1960	Absence seizures only	GI distress, no efficacy for other seizure types

4.2 Second-Generation AEDs (1990s–2000s)

Drug	Year	Mechanism	Key Advantages
Gabapentin	1993	α2δ calcium channel	Minimal interactions, renally excreted
Lamotrigine	1994	Sodium channel blockade	Broad spectrum, favorable cognitive profile
Topiramate	1996	Multiple mechanisms	Broad spectrum, weight loss
Levetiracetam	1999	SV2A binding	Broad spectrum, minimal interactions
Oxcarbazepine	2000	Sodium channel blockade	Better tolerability than carbamazepine
Zonisamide	2000	Multiple mechanisms	Long half-life (once daily)
Pregabalin	2004	α2δ calcium channel	Higher potency than gabapentin

4.3 Third-Generation AEDs (2010s–Present)

Drug	Year	Mechanism	Unique Features
Lacosamide	2008	Slow sodium channel inactivation	IV formulation, PR prolongation
Perampanel	2012	AMPA receptor antagonist	Once-daily, behavioral AEs
Brivaracetam	2016	SV2A (higher affinity)	Lower behavioral AE incidence
Cenobamate	2019	Sodium channel + GABA	High efficacy, DRESS risk
Fenfluramine	2020	Serotonin modulation	Dravet syndrome
Ganaxolone	2022	Neurosteroid (GABA PAM)	CDKL5 deficiency

5. Pharmacological Mechanisms

5.1 Voltage-Gated Sodium Channel Blockers

Drug	Binding Site	Key Features
Phenytoin	Fast inactivation	Narrow TI, nonlinear PK
Carbamazepine	Fast inactivation	Autoinduction
Lamotrigine	Fast inactivation	Slow titration required
Oxcarbazepine	Fast inactivation	Better tolerability
Lacosamide	Slow inactivation	Different binding site

Cenobamate	Fast inactivation + GABA	Dual mechanism

5.2 GABAergic Agents

GABA positive allosteric modulators: Phenobarbital is a **GABA** receptor positive allosteric modulator. It acts on GABA receptors via a site different from GABA, enhancing the action of GABA and extending the open state of the chloride ion channels, allowing more chloride ions to enter and thus causing hyperpolarization and reduction of neuronal excitability to produce anxiolytic, anticonvulsant, and hypnotic effects.Mechanisms for increasing GABA: Pregabalin/Gabapentin (GABA synthesis stimulators), Valproate (GABA synthesis stimulator, GABA transaminase inhibitor), Tiagabine.

5.3 Calcium Channel Modulators

- **T-type calcium channel blockers:** Ethosuximide (absence seizures), Valproic acid, Zonisamide
- **α2δ calcium channel binders:** Gabapentin, Pregabalin (reduces neurotransmitter release)

5.4 SV2A Modulators

- **Levetiracetam:** Binds SV2A, modulating neurotransmitter release
- **Brivaracetam:** Higher SV2A affinity, lower behavioral adverse effect incidence

5.5 AMPA Receptor Antagonist

- **Perampanel:** Selective, non-competitive AMPA receptor antagonist (unique mechanism)

5.6 Multiple Mechanisms Agents

- **Valproic acid:** Sodium channel blockade, GABA enhancement, T-type calcium blockade
- **Topiramate:** Sodium channel blockade, GABA enhancement, AMPA/kainate antagonism, carbonic anhydrase inhibition
- **Cenobamate:** Sodium channel blockade + GABA enhancement

6. Pharmacokinetic Comparison

6.1 Absorption and Bioavailability

Drug	Bioavailability	Food Effect
Phenytoin	Variable, dose-dependent	Yes
Carbamazepine	70-80% (variable)	Yes
Valproic acid	80-100%	Yes
Lamotrigine	>98%	Minimal
Levetiracetam	~100%	Minimal
Gabapentin	27-60% (saturable)	Minimal
Topiramate	~80%	Minimal

6.2 Distribution: Plasma Protein Binding

- **High protein binding (>80%):** Phenytoin, Valproic acid, Carbamazepine, Perampanel
- **Low protein binding (<20%):** Levetiracetam, Gabapentin, Pregabalin, Topiramate

6.3 Metabolism and Hepatic Enzyme Interactions

- **Extensive CYP metabolism (older AEDs):** Phenytoin (CYP2C9/19), Carbamazepine (CYP3A4), Phenobarbital (CYP2C19)
- **Minimal CYP metabolism (newer AEDs):** Levetiracetam (66% renal), Gabapentin (100% renal), Lamotrigine (UGT glucuronidation)
- **Enzyme inducers:** Phenytoin, Carbamazepine, Phenobarbital
- **Enzyme inhibitors:** Valproic acid, Oxcarbazepine (mild)

6.4 Elimination Half-Life and Dosing Frequency

Drug	Half-Life (hours)	Dosing Frequency
Phenytoin	7-42 (nonlinear)	Once or twice daily
Carbamazepine	10-20	Twice or thrice daily
Valproic acid	9-16	Twice or thrice daily
Phenobarbital	50-120	Once daily
Lamotrigine	25	Once or twice daily
Levetiracetam	6-8	Twice daily
Topiramate	21	Twice daily
Gabapentin	5-7	Three times daily
Zonisamide	63	Once daily
Perampanel	105	Once daily

6.5 Clinical Implications

The newer antiepileptic drugs are preferred due to the reasons such as better pharmacokinetics, minimal drug-drug interactions, and an easier schedule of taking medicines, which help to improve medication adherence and minimize any safety risks. It is not necessary to perform routine therapeutic drug monitoring in most cases, thus saving healthcare resources. The new-generation drugs are ideal for use in multi-medicinal cases. Nevertheless, special attention must be paid to the dose adjustments for elderly patients or those with kidney disease, specifically with drugs that are excreted by kidneys like levetiracetam, gabapentin, and pregabalin.

7. Comparative Clinical Efficacy

7.1 Monotherapy in New-Onset Epilepsy

Focal epilepsy:

Several antiepileptic drugs (AEDs) are effective as initial monotherapy for newly diagnosed focal epilepsy. **Lamotrigine** and **carbamazepine** demonstrate comparable seizure-control efficacy; however, lamotrigine is generally better tolerated and is associated with fewer adverse effects, making it a preferred option for many patients. **Levetiracetam** has been shown to be non-inferior to carbamazepine in achieving seizure control and offers advantages such as fewer drug interactions, simpler dosing, and improved overall tolerability. **Oxcarbazepine** provides efficacy similar to carbamazepine while exhibiting a more favorable safety and tolerability profile. Consequently, treatment selection should consider not only seizure control but also patient-specific factors, adverse-effect profiles, comorbidities, and long-term treatment adherence.

Generalized epilepsy:

Valproate continues to be the first-line drug in the management of generalized epilepsy owing to its effectiveness in managing various seizure types, although it may be restricted because of its side effects. Lamotrigine is a good alternative in the management of GTCS and absence seizures; however, it should be avoided in patients with myoclonic seizures because it can exacerbate these conditions. Levetiracetam, which is also a broad-spectrum AED, is efficacious in managing GTCS as well as myoclonic seizures. Ethosuximide is the best choice for childhood absence epilepsy owing to its superior efficacy and safety profile for managing absence seizures.

7.2 Seizure Control and Remission Rates

Drug	12-Month Remission Rate
Valproic acid (generalized)	70-80%
Lamotrigine (focal)	60-70%
Carbamazepine (focal)	60-70%
Levetiracetam	60-70%

Approximately 70% of patients achieve seizure control with the first or second appropriately chosen AED; 30% develop drug-resistant epilepsy.

7.3 Effectiveness by Seizure Type

Seizure Type	Older Preferred	Newer Preferred
Focal	Carbamazepine, Phenytoin	Lamotrigine, Levetiracetam, Oxcarbazepine
Generalized tonic-clonic	Valproic acid	Lamotrigine, Levetiracetam, Topiramate
Absence	Ethosuximide, Valproic acid	Lamotrigine
Myoclonic	Valproic acid	Levetiracetam

Drug-resistant focal	—	Cenobamate, Perampanel, Lacosamide

8. Safety and Adverse Effects

8.1 Central Nervous System Effects

- **Older AEDs:** Phenytoin (nystagmus, ataxia), Carbamazepine (diplopia, dizziness), Phenobarbital (significant sedation)
- **Newer AEDs:** Somnolence common across multiple agents; perampanel (hostility, aggression); topiramate (word-finding difficulty, cognitive slowing)

8.2 Teratogenicity

Drug	Major Malformation Risk	Recommendation
Valproic acid	9-11%	Avoid in women of childbearing potential
Topiramate	4-5%	Caution
Carbamazepine	2-3%	Alternative preferred
Lamotrigine	2-3%	Preferred
Levetiracetam	2-3%	Preferred

8.3 Long-Term Safety

- **Older AEDs:** Phenytoin (gingival hyperplasia, hirsutism, peripheral neuropathy, osteomalacia); Valproic acid (weight gain, PCOS, metabolic syndrome)
- **Newer AEDs:** Topiramate/zonisamide (nephrolithiasis); Gabapentin/pregabalin (weight gain, peripheral edema)

9. Drug Interaction Profile

9.1 Cytochrome P450 Interactions

Drug Type	Effect	Examples
Strong inducers	↓ AED levels, ↓ oral contraceptive efficacy	Phenytoin, Carbamazepine, Phenobarbital
Inhibitors	↑ AED levels	Valproic acid, Oxcarbazepine (mild)
Minimal interaction	No significant CYP effects	Levetiracetam, Gabapentin, Pregabalin

9.2 P-contributing to drug resistance.**Glycoprotein Interactions**

P-glycoprotein (P-gp) is a transporter protein, which is present on the blood-brain barrier and relies on ATP to remove many drugs from entering the brain. Some antiepileptic drugs such as phenytoin, carbamazepine,

and phenobarbital are known to induce P-gp. The increased activity of P-gp results in enhanced elimination of the drugs through the blood-brain barrier and consequently decreases the intracranial level of the affected AEDs by removing them back into the circulation. This phenomenon might explain why some patients fail to gain adequate seizure control despite having therapeutic levels of plasma drugs, leading to pharmacoresistance of epilepsy. Pharmacoresistance occurs in the presence of an adequate dose of anticonvulsant agents. Therefore, the induction of P-gp can be considered one possible factor responsible for the pharmacoresistance of epilepsy. It is important to understand P-gp drug transport as this knowledge might affect the choice of the drug or ways to overcome antiepileptic drug resistance.

9.3 Clinical Implications

The newer antiepileptic drugs, including levetiracetam, gabapentin, and pregabalin, pose a low risk for clinically relevant drug–drug interactions, owing to their poor first-pass effect, limited metabolism through hepatic pathways, and lack of induction or inhibition of cytochrome P450 enzymes. Such a pharmacokinetic advantage renders these newer AEDs especially advantageous in polypharmacy patients. These AEDs are recommended for use in elderly patients, HIV-infected patients undergoing antiretroviral therapy, transplant patients under immunosuppressive therapy, and psychiatric patients requiring psychotropic agents. By avoiding changes in drug levels caused by interaction effects, these AEDs ensure drug effectiveness and minimize side effects.

10. Use in Special Populations

10.1 Pediatric Patients

In the management of epilepsy in children, both efficacy and safety should be taken into account. Levetiracetam has shown effectiveness similar to that of phenytoin in the management of convulsive status epilepticus in children. However, the preference is often given to levetiracetam because it is safer to use and easy to administer. Valproic acid is an efficacious broad-spectrum antiepileptic medication; however, its use in children under the age of two is risky as it increases the risk of serious hepatotoxicity especially in cases where the child has a metabolic disorder. Phenobarbital is another medication used to control seizures; however, this medication affects the neurodevelopment process leading to impaired cognitive function, learning problems and hyperactive behavior among others.

10.2 Geriatric Patients

Safety, tolerability, and fewer medication interactions are the main considerations for epilepsy treatment in older patients. Levetiracetam, lamotrigine, and gabapentin are better options because of their safety, well-characterized pharmacology, and lack of interactions with other medications frequently used by this group. Renal clearance decreases in the aging process by 10–50%, making it necessary to reduce the doses of renally cleared medications. Specific antiepileptic drugs are not recommended for older patients because of various reasons. Phenytoin may lead to toxicity because of its non-linear pharmacodynamics, while phenobarbital is likely to increase sedation and the risk of falling. Topiramate affects cognition and memory.

10.3 Pregnant Women

Effective management of seizures and safety during pregnancy should be achieved when treating patients with epilepsy. However, valproic acid poses high risks for teratogenic effects such as congenital malformations and developmental problems; hence, it should be avoided unless there are no other alternatives. Lamotrigine and levetiracetam are considered safer drugs for use in pregnancy and have a reduced risk of producing congenital malformations. Pregnancy results in a number of physiological changes that affect pharmacokinetics and increase drug clearance. For instance, the clearance of lamotrigine

can be elevated by 200-300% and that of levetiracetam by 60-100%. This leads to lowering of drug levels in the blood and hence less effective management of seizures.**10.4 Hepatic or Renal Impairment**

- **Renal impairment (CrCl <60):** Reduce doses of levetiracetam, gabapentin, pregabalin
- **Hepatic impairment:** Dose adjust lamotrigine, valproic acid, phenytoin; levetiracetam and gabapentin safe.

11. Emerging Drugs

Drug	Mechanism	Indication	Status
Azetukalner	Kv7 potassium channel opener	Focal epilepsy	Phase 3
EPX-100	Clemizole hydrochloride	Dravet syndrome	Phase 2
Vormatrigine	Sodium channel	Focal epilepsy	Phase 3

12. Conclusion

Antiepileptic drugs both old and new have a place in the treatment of epilepsy in the current era. The older AEDs still make effective, inexpensive choices that work well because of their efficacy; yet, their use is limited by the complexity of their pharmacokinetics, narrow therapeutic window, considerable interaction with other medications, and their adverse effects. The newer AEDs are significantly better than the older drugs in terms of pharmacokinetics predictability, tolerability, and safety profile. Levetiracetam and lamotrigine have become favorite choices for women of childbearing potential because of their low risk of causing fetal malformations. Gabapentin and pregabalin demonstrate effectiveness in treating focal seizures and few drug interactions; yet, topiramate causes cognitive problems, perampanel behavioral complications, while the third generation AEDs are expensive. It should be emphasized that medication choice depends on factors such as seizure type and epilepsy syndromes, age and comorbidity status of patients, vulnerability to adverse effects, teratogenic risk, interaction profile, and cost-effectiveness. Both older and newer AEDs can play an important role in the management of epilepsy.

Reference

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342(5):314–319.
3. Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology*. 2012;78(20):1548–1554.
4. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007;369(9566):1000–1015.
5. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy. *Lancet*. 2007;369(9566):1016–1026.
6. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. *Lancet Neurol*. 2009;8(11):1019–1030.
7. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol*. 2006;61(3):246–255.

8. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring. *Epilepsia*. 2008;49(7):1239–1276.
9. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Comparative risk of major congenital malformations with antiepileptic drug monotherapy. *Lancet Neurol*. 2018;17(6):530–538.
10. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD Study). *Lancet Neurol*. 2013;12(3):244–252.
11. Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology*. 2005;64(11):1868–1873.
12. French JA, Perucca E. Time to broaden the horizon of antiepileptic drug development. *Epilepsy Res*. 2009;85(1):1–2.
13. Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. *Nat Rev Drug Discov*. 2013;12(10):757–776.
14. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol*. 2012;11(9):792–802.
15. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the International League Against Epilepsy (ILAE). *Epilepsia*. 2010;51(6):1069–1077.