

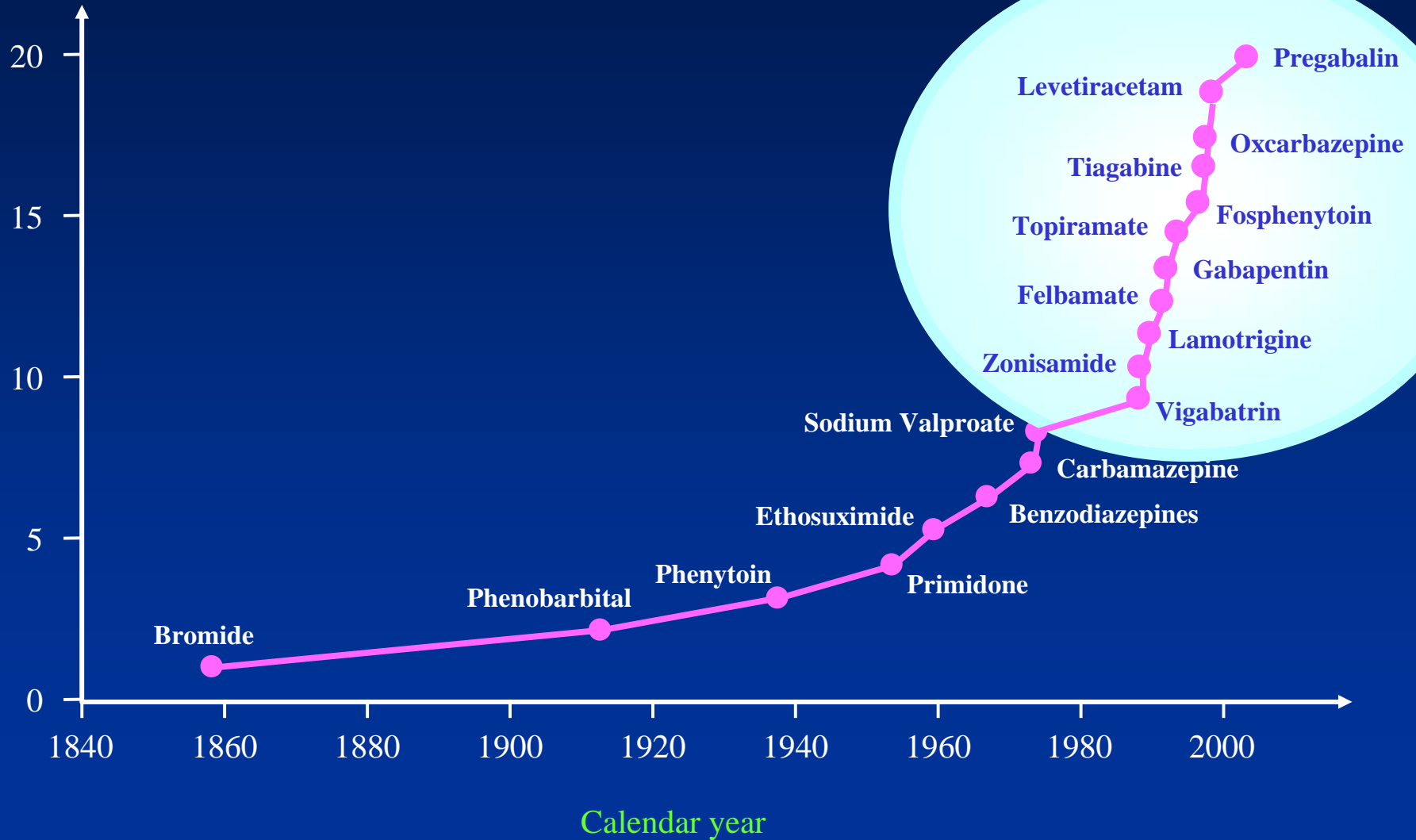
MATCHING DRUGS TO PATIENTS



Professor Martin J Brodie
Director, Epilepsy Unit
University of Glasgow
Glasgow, Scotland

MATCHING DRUGS TO PATIENTS

Antiepileptic drugs



MATCHING DRUGS TO PATIENTS

First choice options

Phenobarbital	}	Established
Phenytoin		
Carbamazepine		
Sodium valproate		

Lamotrigine	}	Modern
Oxcarbazepine		
Gabapentin		
Topiramate		
Levetiracetam		

MATCHING DRUGS TO PATIENTS

There is no reliable evidence to suggest any difference in efficacy between :

carbamazepine and phenytoin

carbamazepine and valproate

phenytoin and valproate

for partial or generalized tonic-clonic seizures

THE COCHRANE LIBRARY

MATCHING DRUGS TO PATIENTS

There is evidence that carbamazepine and phenytoin are better tolerated than phenobarbital but no evidence of a difference between these drugs in controlling seizures

THE COCHRANE LIBRARY

MATCHING DRUGS TO PATIENTS

Randomized, head-to-head, double-blind trials with
modern antiepileptic drugs
(N = 18)

Lamotrigine	versus	Carbamazepine (3), Gabapentin (2), Phenytoin
Oxcarbazepine	versus	Phenytoin (2), Carbamazepine, Valproate
Vigabatrin	versus	Carbamazepine
Gabapentin	versus	*Carbamazepine (2), Lamotrigine
Topiramate	versus	*Carbamazepine, *Valproate
Levetiracetam	versus	Controlled-release carbamazepine

* fixed doses

MATCHING DRUGS TO PATIENTS

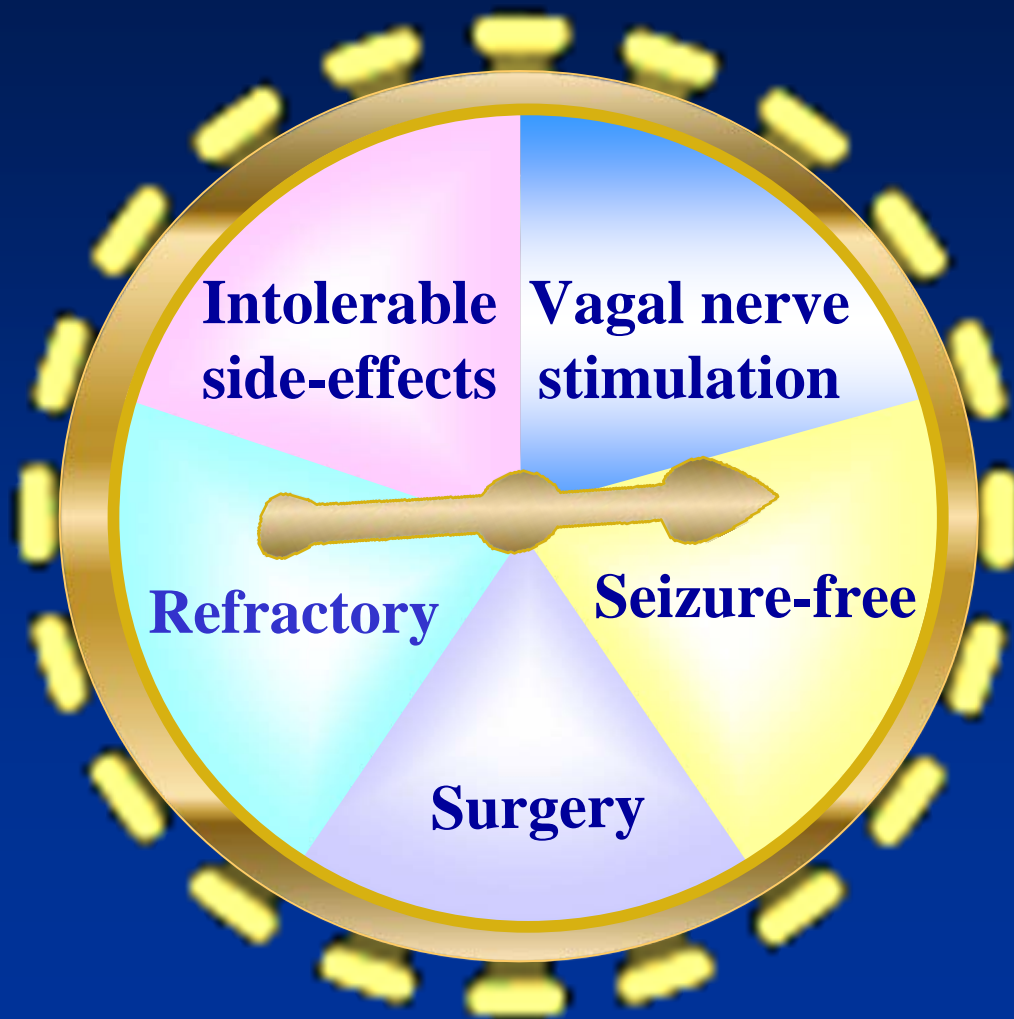
Safety

As there are no major differences in efficacy among first-line antiepileptic drugs, tolerability and longterm safety must be the paramount consideration in patients with often mild newly diagnosed epilepsy

Kwan P, Brodie MJ. Neurology 2003; 60 (suppl 4): S2-S12

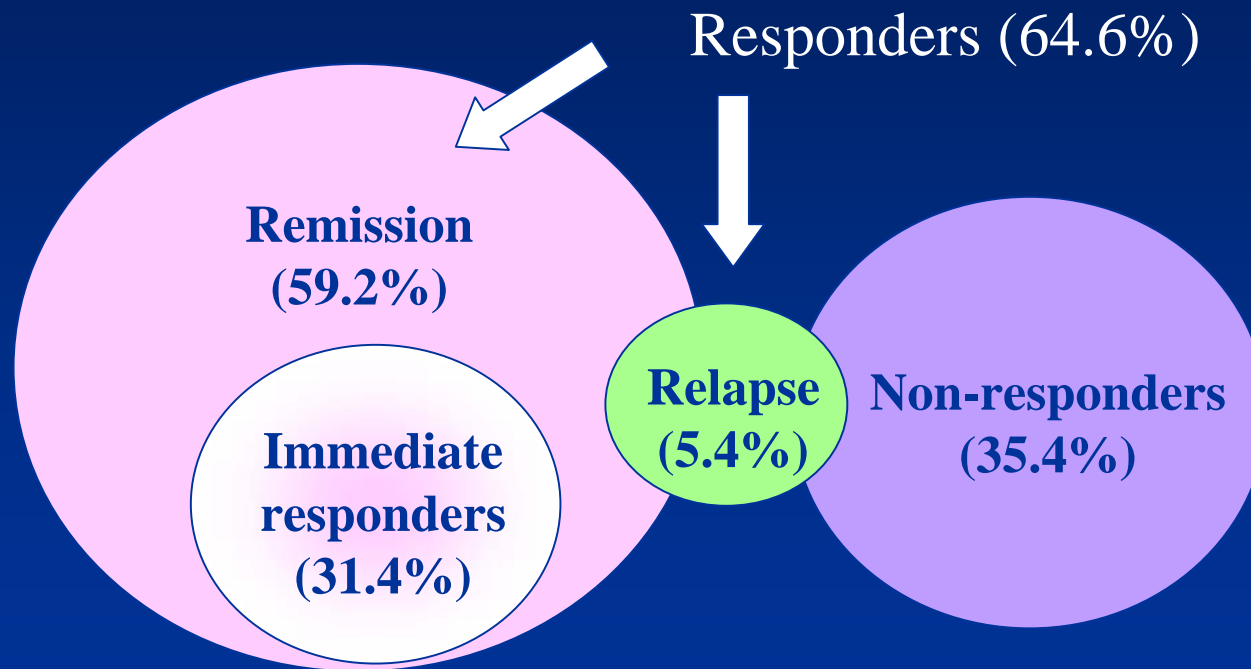
NEWLY DIAGNOSED EPILEPSY

Epilepsy wheel of fortune



NEWLY DIAGNOSED EPILEPSY

Categories of treatment response
(N=780)



NEWLY DIAGNOSED EPILEPSY

Two populations

- ❖ “Winners” (56.1%) who will remit on their first AED or second regimen
- ❖ “Losers” (35.4%) who will never have a useful period of seizure freedom

THESE TWO POPULATIONS ACCOUNTED FOR 91.5% OF ALL PATIENTS WITH NEWLY DIAGNOSED EPILEPSY



Monotherapy - treatment of choice !

MATCHING DRUGS TO PATIENTS

Which antiepileptic drug to chose first?

Pick a drug with a spectrum of activity and side-effects/interaction profile that has the potential to produce seizure freedom without longterm sequelae

MATCH THE CHOICE TO THE PATIENT'S SEIZURES AND/OR EPILEPSY SYNDROME, GENDER, AGE, WEIGHT, PSYCHIATRIC AND OTHER COMORBIDITIES, RISK OF TERATOGENESIS AND CONCOMITANT MEDICATION etc.

COST MUST ALSO BE TAKEN INTO CONSIDERATION

MATCHING DRUGS TO PATIENTS

Antiepileptic drugs























Efficacy

































Exacerbation

ESTABLISHED DRUGS AND SEIZURE TYPES

	PB	PHT	CBZ	VPA	ESM
Partial/generalized					
Tonic-clonic					
Absence					
Myoclonic	?				
Atonic/tonic					

MODERN DRUGS AND SEIZURE TYPES

	GBP PGB	LTG	LEV	OXC	TGB	TPM	ZNS
Partial/generalized							
Tonic-clonic					?		
Absence						 ?	
Myoclonic		 ?					
Atonic/tonic			?				?

DRUG INTERACTIONS



ENZYME INDUCTION

Perpetrators

Phenobarbital

Primidone

Carbamazepine

Phenytoin



Broad spectrum

Oxcarbazepine

Topiramate (>200mg)

Felbamate



CYP3A4

ENZYME INDUCTION

Consequences

Enzyme inducers accelerate the clearance of :

- ❖ many lipid soluble drugs
eg oral contraceptives, warfarin, cytotoxics, antiretrovirals, statins, immunosuppressants
- ❖ some endogenous hormones
eg vitamin D, sex hormones, cortisol
- ❖ other antiepileptic drugs
eg phenytoin, carbamazepine, valproate, ethosuximide, lamotrigine, topiramate, tiagabine, zonisamide

ENZYME INDUCTION

Forty out of 716 children with acute lymphoblastic leukemia on enzyme-inducing AEDs had a worse outcome

	Hazard ratio	95% CI	<i>P</i> value
CNS relapse	2.90	1.01-8.28	0.047
Hematological relapse	3.40	1.69-6.88	0.0006
Event-free survival	2.67	1.50-4.76	0.0009

Relling MV, Pui C-H, Sandlund JT, et al. Lancet 2000;356:285-290

MATCHING DRUGS TO PATIENTS

Interactions with oral contraceptives (OCs)

Reduced
OC levels

Reduced levels
of both

Reduced
AED levels

No kinetic
interactions

Phenobarbital

Lamotrigine

Valproate

Benzodiazepines

Phenytoin

Oxcarbazepine

Gabapentin

Primidone

Levetiracetam

Carbamazepine

Pregabalin

Oxcarbazepine

Tiagabine

Topiramate (>200mg)

Vigabatrin

Felbamate

Zonisamide

MATCHING DRUGS TO PATIENTS

Special populations



MATCHING DRUGS TO PATIENTS

Special populations - teenagers

Generalized seizures
(classify syndrome)

Weight gain
(avoid valproate, gabapentin, pregabalin)

Eating disorder
(avoid topiramate, zonisamide)

Oral contraceptives
(avoid enzyme inducers, remember lamotrigine)

MATCHING DRUGS TO PATIENTS



MATCHING DRUGS TO PATIENTS

Special populations - women

Dysmorphic changes

(avoid phenytoin)

Oral contraceptives

(avoid enzyme inducers, remember lamotrigine)

Teratogenesis

(avoid valproate, phenobarbital)

Ovarian dysfunction

(avoid valproate)

MATCHING DRUGS TO PATIENTS

Foetal anticonvulsant syndrome

- ❖ High forehead
- ❖ Flat nasal bridge
- ❖ Shallow philtrum
- ❖ Long upper lip
- ❖ Thin vermilion border



? DEVELOPMENTAL DELAY

MATCHING DRUGS TO PATIENTS

Special populations - elderly

Underlying neuropathology
(avoid sedation, dizziness, ataxia)

Drug interactions
(avoid enzyme inducers)

Hyponatraemia
(avoid carbamazepine, oxcarbazepine)

Tremor/parkinsonism
(avoid valproate)

MATCHING DRUGS TO PATIENTS

Special populations – learning disability

Multiple seizure types
(use broad spectrum agents)

Behavioural problems
(avoid barbiturates, benzodiazepines)

Weight issues
(use weight relevant drug)

MATCHING DRUGS TO PATIENTS

Comorbidities

Neuropathic pain

Carbamazepine

Oxcarbazepine

Lamotrigine

Gabapentin

Pregabalin

Migraine prophylaxis

Valproate

Topiramate

Essential tremor

Primidone

Topiramate

Anxiety

Gabapentin

Pregabalin

Clobazam

Bipolar disorders

Carbamazepine

Oxcarbazepine

Valproate

Lamotrigine

MATCHING DRUGS TO PATIENTS

An orderly approach

Choose another drug if the first fails due to :

- ❖ rash or other idiosyncratic reaction
- ❖ poor tolerability at low/moderate dosage
- ❖ no improvement in seizure control

RATIONAL DUOTHERAPY

Does it exist?



REPORTS OF “USEFUL” COMBINATIONS

Drugs	Seizures	Reference
VPA+ESM	Absence	Rowan et al, 1983
VPA+CBZ	Partial	Brodie and Mumford, 1999
VPA+LTG	Various	Brodie et al, 1997; Pisani et al, 1999
CBZ+ VGB	Partial	Brodie and Mumford, 1999
LTG+VGB	Partial	Stolarek et al, 1994
VGB+TGB	Partial	Leach and Brodie, 1994
TPM+LTG	Partial	Stephen et al, 1998

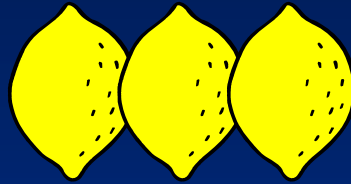
MATCHING DRUGS TO PATIENTS

Mechanistic hypothesis

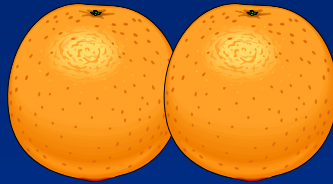
- ❖ Combinations of antiepileptic drugs with similar mechanisms will be no more than additive
- ❖ Combinations of drugs with differing mechanisms have the potential of being synergistic

**BROAD SPECTRUM DRUGS MAY HAVE
ADVANTAGES IN THIS SETTING**

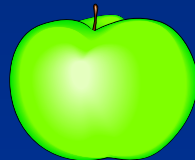
MECHANISTIC DIVERSITY



= primary action



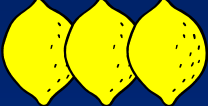




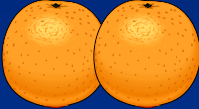

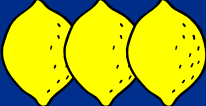

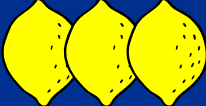


= probable action





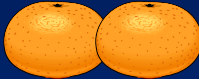
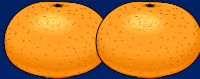
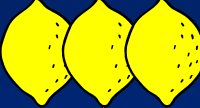
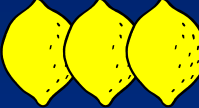







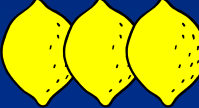








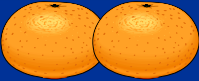
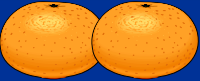


= possible action

MECHANISTIC DIVERSITY

	Na ⁺ currents	Ca ²⁺ currents	K ⁺ currents	GABA transmission	EAA transmission
--	-----------------------------	------------------------------	----------------------------	----------------------	---------------------

Phenytoin					
Carbamazepine					
Sodium valproate					
Ethosuximide					
Phenobarbital					
Benzodiazepines					

MECHANISTIC DIVERSITY

	Na ⁺ currents	Ca ²⁺ currents	K ⁺ currents	GABA transmission	EAA transmission
Felbamate					
Gabapentin/Pregabalin					
Lamotrigine					
Levetiracetam					
Oxcarbazepine					
Topiramate					
Tiagabine					
Vigabatrin					
Zonisamide					

MATCHING DRUGS TO PATIENTS

An orderly approach

If the patient tolerates the first drug well
with a useful but suboptimal response,
combination therapy should be considered
particularly if there is a high pre-treatment seizure
density and demonstrable underlying pathology

MATCHING DRUGS TO PATIENTS

An orderly approach

If the patient responds to the first drug, increase the dose by increments towards the limit of tolerability

THEN

If seizure control is greatly improved on a high dose, add another with different mechanisms of action

CONSIDER REDUCING THE DOSE OF THE ORIGINAL DRUG ESPECIALLY IF THE PATIENT ALREADY HAS OR DEVELOPS SIDE-EFFECTS

MATCHING DRUGS TO PATIENTS

An orderly approach

Use as maintenance the drug that seems to be the best choice for that patient

THEN

Try a sequence of drugs with different, possibly multiple, mechanisms of action

THEN

Consider adding a third AED with potentially complementary pharmacological properties

DRUG BURDEN IS A FUNCTION OF DOSE AS WELL AS NUMBER OF DRUGS

MATCHING DRUGS TO PATIENTS

Broad spectrum drugs

Sodium valproate

* Lamotrigine

* Topiramate

Levetiracetam

Zonisamide

* Take care in myoclonic epilepsies

* Take care in absence epilepsies

MATCHING DRUGS TO PATIENTS

Narrow spectrum drugs

Pregabalin

Oxcarbazepine

Tiagabine (non-inducers)

Carbamazepine

Phenytoin

Gabapentin

(Phenobarbital)

(Ethosuximide)

MATCHING DRUGS TO PATIENTS

Third-line drugs

Acetazolamide

Clobazam

Piracetam

Tiagabine (inducers)

(Vigabatrin)

(Primidone)

(Clonazepam)

MATCHING DRUGS TO PATIENTS

The search for seizure freedom

Right patient(s)

Right drug(s)



MATCHING DRUGS TO PATIENTS

Conclusion

A wide range of established and modern antiepileptic drugs with different mechanisms of action, pharmacokinetics, spectra of efficacy, side effect and interaction profiles are now available for the treatment of epilepsy

**WE SHOULD MAKE AN EFFORT TO CHOOSE THE
BEST MONOTHERAPY OR COMBINATION REGIMEN
FOR EACH INDIVIDUAL PATIENT**

MATCHING DRUGS TO PATIENTS

Conclusion

Consider: side-effects
 work and sleep
 mood and wellbeing
 sexual function

AN HOLISTIC APPROACH IS RECOMMENDED USING
A WIDE RANGE OF ANTIEPILEPTIC DRUGS

MATCHING DRUGS TO PATIENTS

Conclusion

An orderly approach to the pharmacological management, and, when appropriate, surgical workup of each epilepsy syndrome will optimise the chance of perfect seizure control and help more patients achieve safer and more fulfilled lives

**A PALLIATIVE APPROACH IS NECESSARY IN
PATIENTS WITH TRULY REFRACTORY EPILEPSY**