

Anticonvulsants, cognition and behaviour in children with epilepsy

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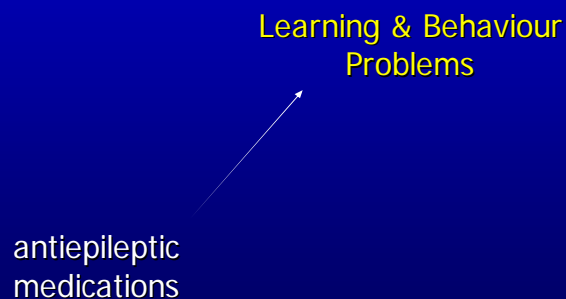
Objectives

- Evidence from clinical trials
- Evidence from pregnancy
- Experimental models of epilepsy
- Predictable cognitive side effects
- Ways to minimise cognitive and behaviour side effects
- Impact of comorbidities on choice of drug

Definitions

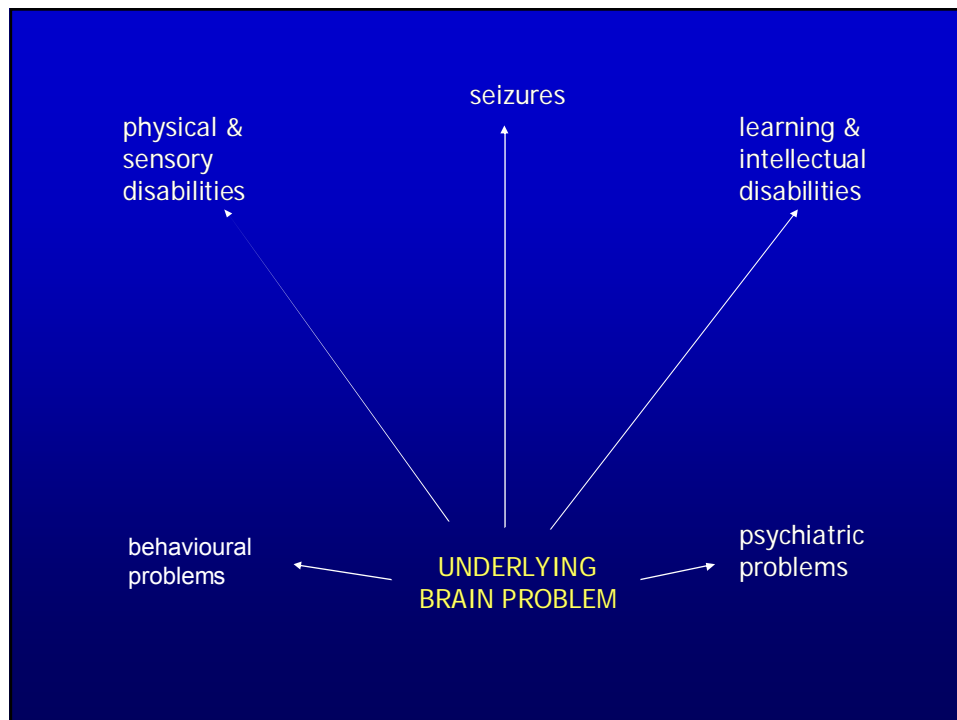
- Behaviour
 - Perception, experience and expression of emotions, Level of energy and motivation
 - Understanding of social situations, Ability to react to dynamic situations, Autonomic responses
- Cognitive functions
 - Attention, vigilance, speed of intellectual functions
 - Arithmetic and linguistic skills, processing of sensory information
 - Processing of sensory information
 - Learning, memory, coordination, speed of motor responses, visuospatial abilities

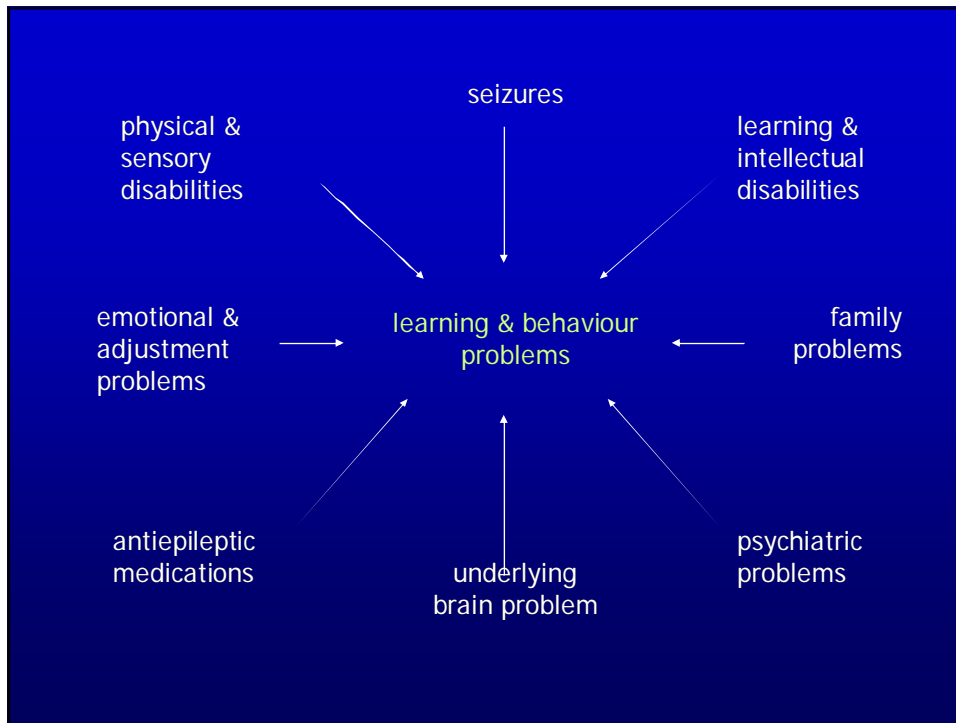
Parent's perception of the situation



Cognitive and behavioural problems in children with epilepsy

- Higher prevalence compared to the norm
Multiple factors are at play
 - Seizure frequency, duration and severity
 - Persistent epileptiform activity
 - Comorbid physical and sensory disabilities
 - Age and the maturational state of the brain
 - Underlying lesion causing the epilepsy
 - Genetic factors
 - pts with ep have baseline IQ than controls
 - lower IQ and sibs of sympt pts have lower IQ than sibs of those with idiopathic ep
 - Medications
 - Psychosocial consequences of epilepsy





Reported SE

- Somnolence
- Psychomotor slowing
- Speech disorders-verbal dysfluency
- Poor Concentration
- Inattention
- Memory problems

The pitfalls with evidence obtained from clinical studies

- Lack of prospective studies
- Spontaneous fluctuations in cognitive performance occur in children with epilepsy
- The negative effects of uncontrolled seizures and persistent EEG abnormalities on cognition*
- The positive effect of seizure reduction and EEG on cognition
- Extrapolation of data from healthy volunteers
- Attributing cognitive improvements or deterioration to the drug by default
- Comparisons in drugs that are not at equivalent doses
- Small sample size and methodological problems

*Marston et al Devel Med Child Neurol 1993;35:574

Study design

- Healthy volunteers
 - Different cerebral substrate
- Comparisons between 2 or 3 drugs
- Add on studies comparing w or w/o placebo
Low versus high dose of one AED
- Prospective studies before and after introduction of AED monotherapy
- Prospective studies before and after discontinuation of AED monotherapy

Before and After starting Rx

- Williams Epilepsia 1998
 - No difference at baseline or a change in cognitive profile and behaviour incl attention, memory, complex motor speed and behaviour problems compared with the IDDM group
- Stores et al Arch Dis Child 1992 Newly diagnosed epilepsy Rxed with CBZ and VPA n=63 cf normal controls
 - No significant difference in IQ at baseline and following 12 months of Rx btn children with epilepsy and controls
 - Attentional and visuomotor problems in both Rx grps
 - Hyperactivity and attentional problems more common in pts with epilepsy at baseline but no worse following AED Rx

Idiopathic Epilepsy before and after

- Mandelbaum et al Devel Med Child Neurol 1997 Newly Dx idiopathic epilepsy n=43 No comparison control grp
 - Controlled for underlying aetiology, seizure type, socioeconomic status
 - No difference at baseline btn idiopathic generalised and focal epilepsy but children with gen non convulsive (absence) epilepsy had lower cognitive scores than those with gen convulsive sz
 - No significant deterioration in cognitive function on assessments 6 and 12 mo following commencement of AED Rx
- Seidel et al J Child Neurol 1999;14:716 Newly Dx BFEC n=10 Rx with CBZ cf 14 controls
 - Cognitive function no different at baseline to controls
 - Deterioration in memory function
 - No change in WISC, attention, language, motor skills or behaviour

Idiopathic Epilepsy before and after

- Forsythe et al Devel Med Child Neurol 1991;33:524-34
 - Newly diagnosed epilepsy n=64 CBZ, PHT, VPA
 - Assessed visual and auditory memory, vigilance, concentration, speed of info processing, WISC
 - Carbamazepine adversely affected memory and correlated with higher serum levels but VPA and PHT did not.
 - Transient effects of CBZ and PHT on speed of info processing but no longer evident on retesting at 6 and 12 mo
 - No effect on IQ or other cognitive parameters
 - CONCLUSION CBZ HAD MOST AND VPA LEAST SE

Before and After

- Doesn't eliminate effect of ongoing szs or sz redn
- Phenobarb
 - memory, concentration, sometimes settle with time Camfield, Hellstrom sometimes cognitive problems persisted after D/C Farwell
- CBZ or VPA vs controls (Stores)
 - More probs at baseline in children with epilepsy
 - But no difference after 12 months of Rx compared to controls
- CBZ or VPA or PHT vs contols(Forsythe)
 - Modest cog effects, CBZ worse than VPA but no diff later on at 12 mo
- Effect of seizure type and med on cog and behav (Mandelbaum)
 - Baseline func higher in pts with focal seizures
 - No deterioration 6 and 12 months following Rx
- BFEC and CBZ Seidel
 - Subtle difference in memory and psychomotor speed after starting Rx

Phenobarbitone (Devinsky r/v)

- Placebo RCT FS PB Camfield
 - irritability, fussiness, sleep disturbance
- DBRCT PB vs valproate in children with epilepsy Vinning Pediatrics 1987
 - PB had a more significant affect on FSIQ, attention, short term learning, fluency and behaviour
- Placebo RCT in febrile seizures PB n=217 Farwell NEJM 1990
 - Mean IQ the same for the 2 grps at baseline but 8.4 points lower after 2 yrs of Rx and didn't completely normalise, 6/12mo following DC (5.2 pts lower) but authors state this is NSS
- Retesting of 139 3-5 years later Sulzbacher et al Clin Pediatr 1999;38:387-94
 - Non signif difference in IQ (3.71 pts) on Stanford Binet
 - Effect persisted in language develop (reading standard scores) on retesting 3-5 yrs later
 - Suggests drug induced decreased cognitive function may not be recoverable at an older age.
- Other small studies have shown this effect is reversible (Riva et al Ped Neurol 1996)

Before and after coming off drugs

- Aldenkamp Neurology 1993;43:41-50 n=83
- D/C of VPA, CBZ, PHT cf age/educational matched controls (did not have formal IQ assessments) 12 tests
- Speed measures (finger tapping, simple reaction time, binary choice reaction)
 - Improvement following D/C
- Central cognitive processing Information processing and attention
- Memory function
- At baseline PHT had more effect on motor and mental speeds than other drugs
- Finger tapping (motor speed) was the only statistically signif improvement of baseline (psychomotor function) (only 1 of 12 cognitive tests)
- Improved alertness, concentration, memory, psychomotor speed shown with D/C of PHT, VPA and CBZ but NSS cf improvement in controls suggesting a retesting effect
 - Problems with practice and control grp performed better on repeat testing
- Improvements in epilepsy grp were not significantly different from change observed in matched controls
- Group differences between epilepsy and control groups persisted following D/C of Rx
- CONCLUSION AED effect on cognitive function is limited

The older drugs-summary

- Phenobarbitone has been shown in some studies to have long lasting effects on academic performance
- Carbamazepine may impact on memory without affecting academic performance (Forsythe)
- All have cognitive side effects but greater for PB and PHT than for CBZ and VPA
- The difference between PHT, CBZ and VPA is small
- Irrespective of drug used polypharmacy has a more severe impact on cognition

Loring DW Review Neurology 2004 kids

- PB may decrease IQ and P300 latency
- CBZ well tolerated and does not affect IQ but may affect memory and attention
- PHT has a small effect on IQ, memory and processing speed
- VPA fewer effects than PHT or CBZ in one study

The newer drugs

- Side effects are as important as efficacy in influencing "retention rate" with the newer AEDs
- At one year
 - TPM 55%
 - LTG 60%
 - GBP 45%
- At three years ~35% for all drugs

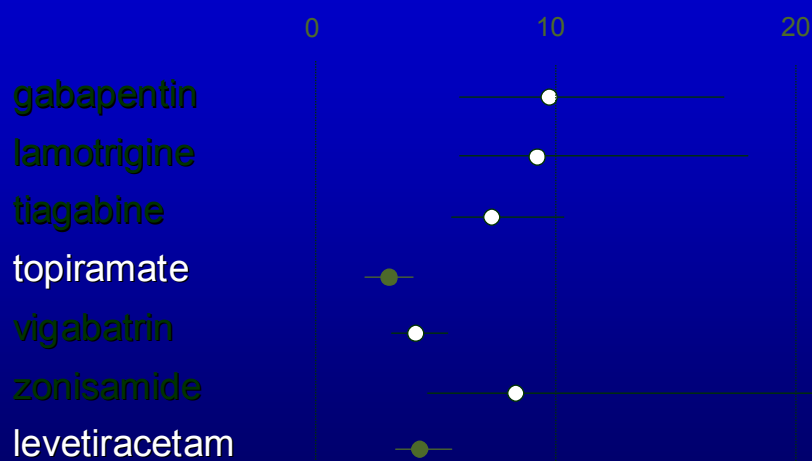
Add on

- Aldenkamp LTG add on to CBZ
 - No impairment of cognitive function
- Leach GBP
 - Increased drowsiness but no effect on psychomotor function or memory
- Burton TPM
 - Effect on attention

Aldenkamp 2003 Epilepsia 2003;44:21-9

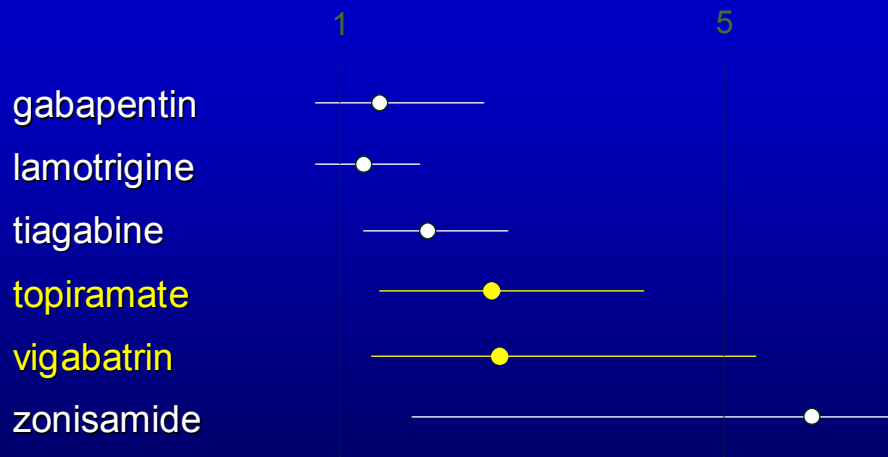
- LTG and OXC have favourable cognitive profiles and unlikely to have a significant effect on cognitive function
- TPM has a less favourable cognitive and behavioural profile but side effects can be reduced by slow titration Aldenkamp et al Epilepsia 2000;41:1167 (cog) and Mula et al Epilepsia;44:2003:659 (behav) adult studies

Comparative efficacy of new AEDs



numbers needed to treat to get one responder from RCTs. *Elferink et al., Lancet 1997*

Comparative tolerability of new AEDs



odds ratio for **withdrawal** relative to placebo from RCTs *Marson et al., Lancet 1996*

Cognitive profile of the new AEDs

- Aldenkamp *Epilepsia* 2003;44(Suppl 4):21-9
- Table
- Cognitive SE in healthy adults
 - Meador *KJ Epilepsy Research* 2006;68:63-7
 - GBP better than CBZ
 - LTG better than CBZ
 - OXC better than PHT
 - LEV better than OXC better than CBZ
 - TGB no worse than Placebo
 - GBP better than TPM
 - LTG better than TPM

The neuropsychological effects of in utero AED exposure

- AEDs can produce "behavioural" teratogenesis at doses lower than that required to produce anatomical teratogenesis
- Neuropsychological assessment on 249 children aged 6-16 born to mothers with epilepsy
- Controlled for maternal IQ and socioeconomic status
- Children exposed to valproate were more likely to have IQ below 69 (22% cf CBZ 8%, Polytherapy 7%) and have memory impairment when compared to children exposed to other drugs or not at all
- Other predictors of low verbal IQ were no. of TC seizures during pregnancy and mother's IQ

Vinten J Neurology 2005;64:949

Does early post natal exposure to AEDs have a long term effect on cognition

- Neonatal rat brain is similar to human fetal brain in last trimester
- Dose dependent apoptotic degeneration has been described in the developing rat brain P5-7 in response to exposure to AEDs including PHT, CBZ, VPA, VGB, CZP
- Reduced expression of neurotrophic factors and beta estradiol
- Newer drugs Apoptosis can be seen with TPM but only at v high doses (Glier 2004) and this effect not seen with LEV (Kim 2004)

Phenobarbitone

- P5-P18 Rat pups injected with phenobarb
- Decreased brain weight, DNA, RNA, protein and cholesterol concentrations (Diaz et al Biol Neonate 1977)
- Hinders brain growth through the inhibition of neuronal protein synthesis
- Rats treated Kainic Acid and then phenobarb had greater disturbances in memory, learning and activity levels than those that received KA alone (Holmes r/v)
- Disrupts cholinergic transmission in the hippocampus
- Reduction in purkinje and granule cells in hippocampus and pyramidal and granule cells in hippocampus
- Suggests there should be a change in practice in NICUs and that PB should not be used as a first line agent for Rx of HIE, ?TPM

Kaindl and Sankar/Holmes reviews Experimental Models

- No convincing experimental data that PHT and CBZ affect cognition when given at an early age.
- BZP can affect memory and learning in rats possibly related to an effect on attention
- Subteratogenic doses of valproate in rats may cause microcephaly and behavioural changes (deficits in spatial learning and altered locomotor activity) in rodents
- Bolanos P36-75 (correlates with prepubescent children) KA model Rx with PB and VPA
 - Following D/C of drugs PB or saline Rx rats were impaired in learning (visuospatial memory) but VPA rats had no deficits

TPM may be protective in the developing brain

- P20 rats with lithium induced neonatal seizures Rats Rxed with 4/52 of TPM had improved visuospatial performance cf to saline Rx rats
- Weanling rats subjected to Status epilepticus TPM treated rats perform better in water maze
- Long term admin of TPM in the normal developing brain does not impair cognitive performance
- Might be neuroprotective in the developing brain in neonatal models of HIE

Gabapentin

- KA induced SE P35 rats Rx with GBP or saline
- Tested after tapering drugs
- Reduced seizures and hyperactivity in GBP Rxed rats cf saline Rxed controls
- No difference in performance in water maze or emotional responses btn GBP and N saline Rxed controls
- Conclusion: GBP has beneficial effect following SE and does not contribute to impairment or enhancement of learning

- Apoptosis-physiological programmed cell death
 - There are periods in pre and post natal human brain development where exposure to AEDs may cause cells to commit suicide
- AEDs can impair cell proliferation and differentiation, synaptogenesis, synaptic plasticity, cell migration and axonal arborisation (no ref given and state that not systematically studied)

Holmes and Sankar Preclinical data

- AED Modulation of ion channels and neurotransmitters and second messengers to reduce seizures interferes with normal brain function in other ways
- Limitations of initial testing of new compounds for side effects
 - Choice of animals with regard to health and age
 - Immature rats are rarely used in the initial screening of AED compounds
 - Screening for toxicity involves tests that assess motor coordination rather than cognition and memory

Mechanism of action may predict side effects

- The glutaminergic system participates in spatial cognitive processes
 - TPM blockade of glutamate mediated Na currents at non NMDA (AMPA and Kainate) sites may explain its cognitive effects.
 - Double edged sword, interfere with the consolidation of memory and learning but they may offer neuroprotective effects
- Augmentation of GABAergic inhibition may have the greatest impact on learning through impaired vigilance and attention
 - May explain barbituates, BZPs, VGB, TGB
- Drugs acting primarily by blocking voltage gated Na channels have minimal effect on cognition and behavioural in animal models

Mechanism of Action

Drug	Na+ Blockade	↑ GABA	↓ Glutamate	Ca+ Channel Blockade	Carbonic Anhydrase Inhibition	Unknown
CBZ	✓					
PHT	✓	✓				
ESM				✓		
BZP		✓				
PB	✓					
VPA	✓	?				
LTG	✓		✓			
GBP						✓
VGB		✓				
TGB		✓				
TPM	✓	✓	✓		✓	
OXC	✓					
LEV						✓

Side Effects

- Predictable (Dose related)
 - Often correlate with serum drug levels
 - Non specific CNS side
 - Specific for each anticonvulsant
- Idiosyncratic behavioural reactions
 - Not predictable based on known pharmacological effect
 - Can be related to rapid introduction or rate of increase in dose

Predictable CNS Side Effects

- Drowsiness, Ataxia, Diplopia, Headache, Nausea
- Psychomotor slowing, poor concentration, cognitive and memory problems, slowed processing speed
- Often difficult to separate from underlying aetiology, epileptic activity on EEG and effects of seizures

Idiosyncratic CNS effects

- Extrapyrarnidal
 - Facial hyperkinesia (CBZ)
 - Choreoathetosis (PHT)
 - Dyskinesia (PHT, VPA, ESM)
 - Epileptic and non epileptic myoclonus (CBZ, PHT, VGB, ? GBP, ? LTG)
- Behavioural side effects
 - Psychosis with vigabatrin
 - Paradoxical agitation with phenobarbitone
 - Aggression
 - Irritability and mood disturbance

Screening for side effects

- Routine screening for side effects in asymptomatic patients is of doubtful value
- Routine screening is probably useful following initiation of therapy
- If abnormal then reasonable to monitor
- Screening does not predict severe idiosyncratic reactions

Comorbidities

- ADHD Up to 40% of pts with epilepsy
 - Phenobarbitone and benzos can exacerbate symptoms
- Psychiatric disorders
 - Depression 25% of adolescents
 - Avoid BZP and PB
 - Anxiety
 - Thought disorders
 - Positive mood stabilising effect VPA, OXC, LTG, GBP

Comorbidities

- Autism
 - Positive (VPA, LTG, LEV) and negative behavioural effects described with AEDs
- Migraine
 - 20% of children with epilepsy have migraine
 - More common in BFEC (BRE and BOEC)
 - Positive (VPA, LTG, TPM, GBP)
- CP epilepsy is five times more common affecting 15-60% of children

Behavioural SE more common in children with ID

- Behavioural problems
 - Prevalence 6% N pop, 12% non CNS physical deformities, 29% uncomplicated Sz, 38% with CNS damage, 58% with seizure and CNS damage
 - More common than other chronic diseases like IDDM, asthma
- PB
 - Mental dulling, depressive symptoms, and behavioural problems
- Gabapentin
 - Hyperactivity, aggression, irritability, aggression
- Lamotrigine and Levetiracetam
 - Aggression, agitation reported but other studies show improvements

Conclusions

- Side effects unlikely in pts on monotherapy
- Higher doses and polytherapy are more likely to be associated with side effects
- Confounding issue is that patients with symptomatic epilepsy or uncontrolled seizures are more likely to be on polytherapy
- Intrinsic and environmental factors play a more significant role in predisposing certain children with epilepsy to cognitive and learning problems

Conclusions

- All the older AEDs have some impact on cognitive function but the effect is usually mild to moderate except for phenobarbitone
- Except for phenobarbitone, prospective studies show not a long lasting effect on cognition although data from pregnancy is concerning
- Children with epilepsy more likely to have cognitive problems than normal controls but these problems do not get worse after starting AEDs or get better on stopping AEDs suggesting AEDs have a limited impact on higher order cognitive function

Conclusions

- Higher order cognitive deficits including modest effects on attention, memory, concentration, processing speed and behaviour have been well described with AEDs
- The higher the dose the more likely they are to occur
- There is some evidence that phenobarbitone can affect IQ but prospective studies have not shown significant deterioration in IQ on formal psychometric testing for other drugs.
- The potential cognitive and behavioural side effects of the newer anticonvulsants have not been studied in a systematic fashion

Conclusions

- Side effects can be minimized by having a good knowledge of pharmacokinetics and anticonvulsant drug interactions and synergistic effects.
- Use of lower dose combination therapy of drugs with synergistic actions may decrease the likelihood of side effects encountered with higher dose monotherapy.
- Knowledge of idiosyncratic side effects of individual drugs may influence choice of therapy in children with specific comorbid disorders.