

Prescribing for childhood epilepsy

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Disclosures

- Received payment for educational meetings:
 - Pfizer
 - GSK
 - UCB Pharma
 - Janssen-Cilag

Many issues

- Prescribing anticonvulsants in children
 - How do YOU decide
- Integrating benefits and risk
- Long term safety data
- Special issues in the very young
 - AED's and the developing brain
- Off label prescribing
- Quality Use of Medicines (QUM)

- 13yo girl with X2 nocturnal generalised tonic clonic seizures
- MRI normal
- EEG ? Generalised epileptic activity but left frontal maximum
- Parents and child want treatment

WHAT DRUG??

How to make this decision?

- Meta-analysis of RCT (Cochrane)
- Individual RCT
- Expert consensus guidelines
- Ask a neurologist
- Personal experience
- Nice lunch



BROWSE

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[Intervention Review] Carbamazepine versus valproate monotherapy for epilepsy

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[Intervention Review] Carbamazepine versus valproate monotherapy for epilepsy

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Editorial group: [Cochrane Epilepsy Group](#).

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Abstract

Background

Carbamazepine and valproate are drugs of first choice for epilepsy. Despite the lack of hard evidence from individual randomized and carbamazepine for partial epilepsies.

Objectives

To overview the best evidence comparing carbamazepine and valproate monotherapy

Search strategy

We searched the Cochrane Epilepsy Group's Specialized Register (27 July 2007), the Cochrane Central Register of Controlled Trials. No language restrictions were imposed. We also contacted pharmaceutical companies and researchers in the field.

Selection criteria

Randomized controlled trials comparing carbamazepine and valproate monotherapy for epilepsy

Cochrane review

- Plain language summary

Carbamazepine versus valproate monotherapy for epilepsy

No reliable evidence to distinguish between carbamazepine and valproate for partial onset seizures and generalized onset tonic-clonic seizures.

ILAE guidelines Rx of epilepsy

- Absence of rigorous comprehensive adverse effects data makes it impossible to develop an evidence-based guideline
- Especially alarming lack of well-designed, RCTs for children.

Epilepsia, 47(7):1094–1120, 2006

International League Against Epilepsy (ILAE)

Expert consensus guidelines

- Australia Therapeutic Guidelines (Neurology)
 - Focal epilepsy:
 - First choice :Carbamazepine
 - If fails, valproate or phenytoin.
 - 3rd choice GBP LTG LEV OXC TPM etc.
 - Generalised epilepsy (JME)
 - Valproate
 - 2nd choice lamotrigine
 - 3rd TPM LEV CLZ

Left with....

- Ask a neurologist
- Personal experience
- Nice lunch

New better than old??

- *American Academy of Neurology*
 - New versus Old AED's
 - **Equivalent** efficacy and side effects

<http://www.neurology.org/cgi/content/full/62/8/1252>

Questions about a **NEW** drug...

- *Does it work?* **BETTER?**
- *Is it safe?* **SAFER?**
- *Are overall benefits worth the overall risks?* **IN CHILDREN**
- *Is it worth the cost?* **CHEAPER?**



...can we afford it?

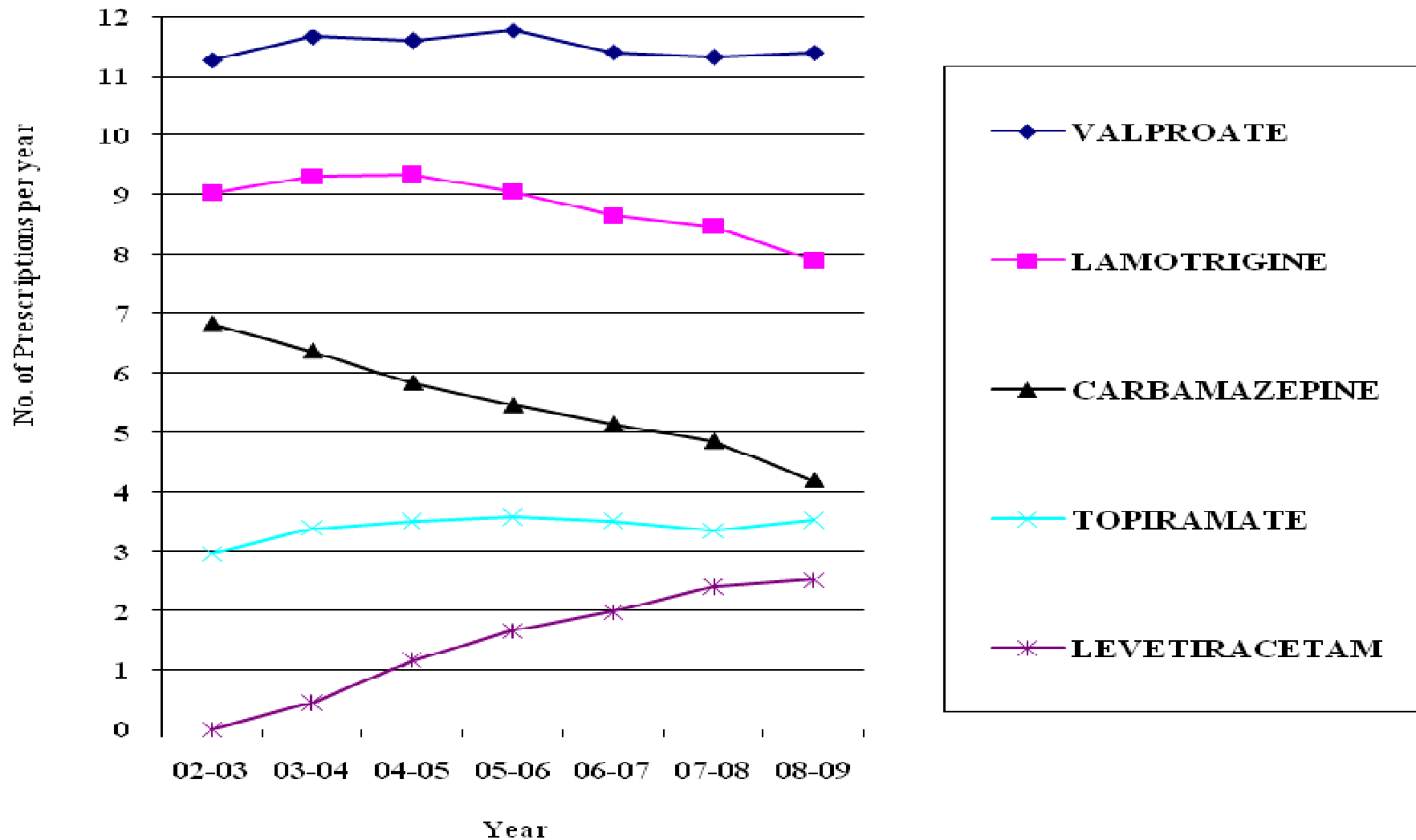
- Are we prescribing appropriately?

Study of paediatric AED prescribing

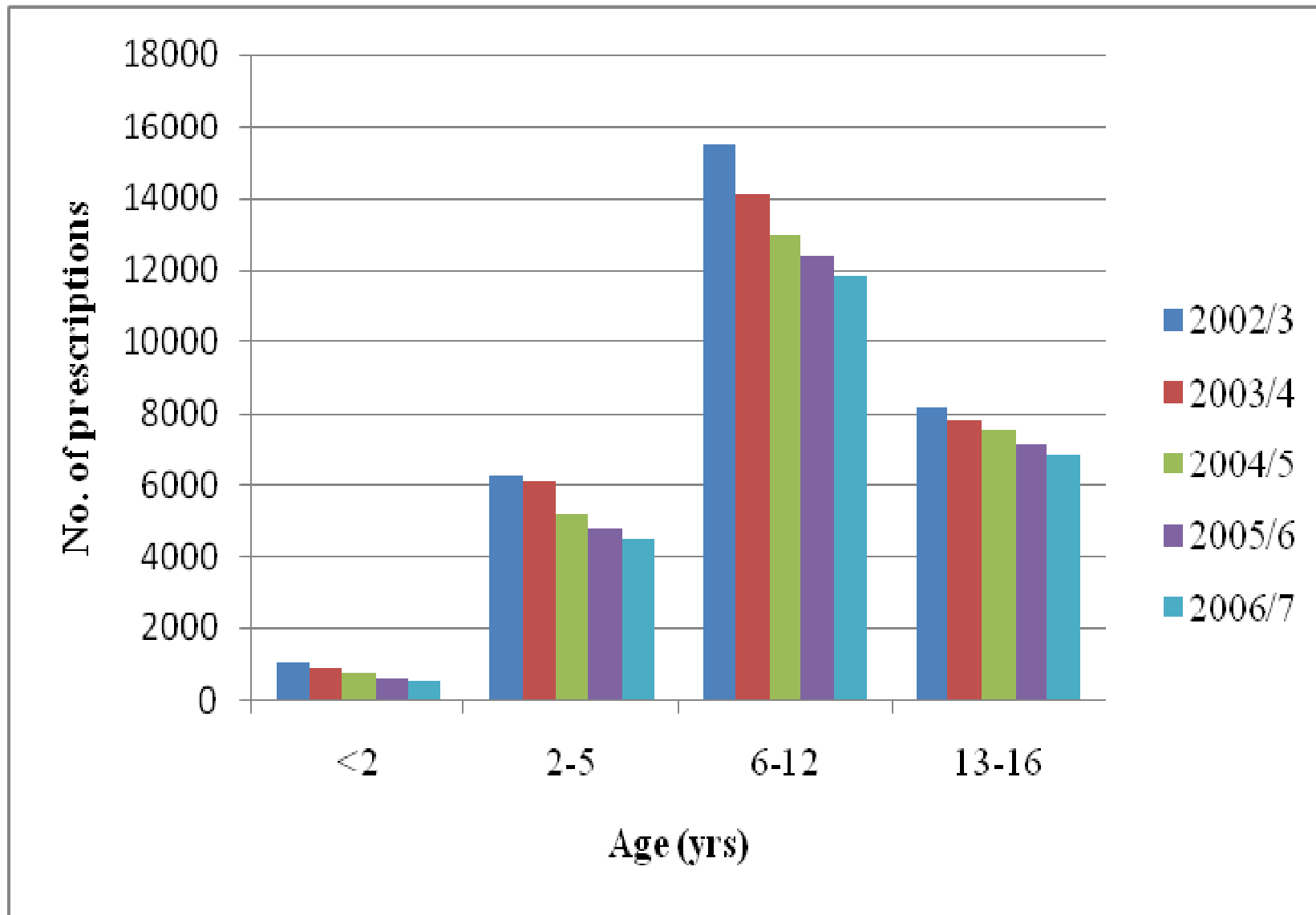
- National data AED's dispensed from community pharmacies from the Drug Utilisation Subcommittee (DUSC), Department of Health and Aging.
- AED's dispensed 2002-2009 to evaluate prescribing trends for the population aged 0-16 years.

Cohen S, Lawson J, Graudins L, Pearson S, Gazarian M submitted

AED prescribing per 1000 pop.



Carbamazepine prescribing trends for 0-16 year old children (2002-2007)



Study of prescribing patterns

- Significant decrease in CBZ scripts ~36%
- Marked increase in the new AED's
- Clinical and economic implications

Gazarian M. Off-label use of medicines in the paediatric population: recommendations for assessing appropriateness. Discussion paper for consultation, [WHO Expert Consultation on Essential Medicines for Children, 9-13 July 2007, Geneva]
http://archives.who.int/eml/expcom/children/INDEX_children_07-2.htm

- Is there high quality evidence supporting this drugs use in children?
 - Clinical effectiveness
 - Long term safety
- High rates ADR's in off label use
- Off label use compounds the problem

Our 13yo girl

- Okay, Okay I will use VPA
- Supported by the guidelines
 - First or second line for both focal and generalised
- In line with QUM principles

American Epilepsy Society

- Valproate should not be prescribed as first-line therapy for any indication in women of childbearing age

Drug	Mean IQ	95% Confidence Interval	P Value
Valproate	89	—	—
Carbamazepine	98	2.8 - 5.4	.009
Lamotrigine	102	6.4 - 18.6	.003
Phenytoin	97	0.2 - 15.5	.04

***Meador KJ, Baker GA, Browning N, et al. N Engl J Med 2009;360:1597-1605.
Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs.***

Aussie guideline

- Valproate should be avoided in reproductive women wherever possible. When it is unavoidable, the lowest effective dose should be used. It should not exceed 1000 mg/day in divided doses.
- *<http://www.australianprescriber.com/magazine/31/3/70/2/>*

Cecilie M Lander, A/Professor of Neurology, U of Queensland

Back to the case...

- Now don't want to start valproate.....
- Mmmm QUM, QUM..
- Carbamazepine??

Let's start Tegretol

- The girl is of Chinese racial background.
- No worries??.....mate.

FDA ALERT 12/12/2007

- **Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with HLA-B*1502.**
- **This allele occurs almost exclusively in patients with ancestry across broad areas of Asia.**
- **Patients with ancestry from these areas should be screened before starting treatment with carbamazepine.**
- **If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions.**

- Did you know this??

Epilepsy Society of Australia 09

- **ESA Recommendations**
- In patients of Han-Chinese ethnicity, testing for HLA-B*1502 should be considered prior to prescribing carbamazepine for the first time. The decision to test or not needs to be balanced by test availability, timeliness of the results and urgency of treatment.
- If the patient tests positive for HLA-B*1502, do not use carbamazepine or phenytoin unless the potential benefit outweighs the increased risk of Stevens-Johnson syndrome (SJS).

http://www.epilepsy-society.org.au/pages/SJS_HLA.php

Litany of problems

- Lack of good data
- “Guidelines” not up to date
- Poor communication of adverse events
- Even drugs available for 40+ years
 - New problems arise
- New drugs always look good
 - No long term safety data

New drug lessons

- Lamictal: Marketed as “The womens drug”
 - OCP reduces LTG levels by 50%
 - Modest decrease in levonorgestrel
 - No safer in pregnancy
 - Not great for breastfeeding
- Vigabatrin
 - 10 years of use before visual field defects noted.



Catch the latest *next autumn*



is for Kids.