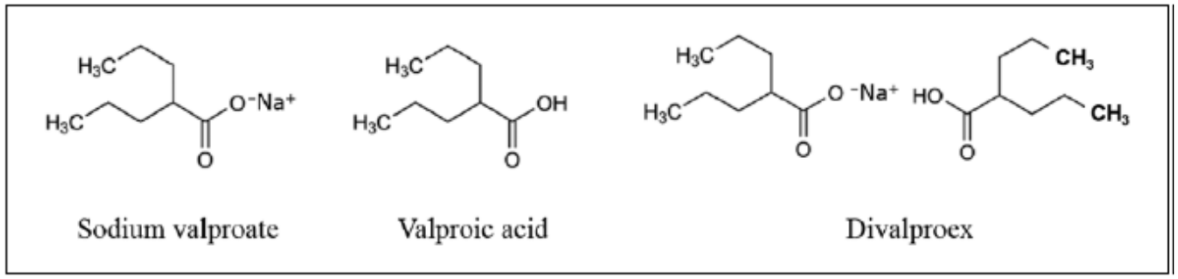
Valproate in women of child bearing potential: efficacy, risks and alternatives

Dr Jennifer Burgess ST1

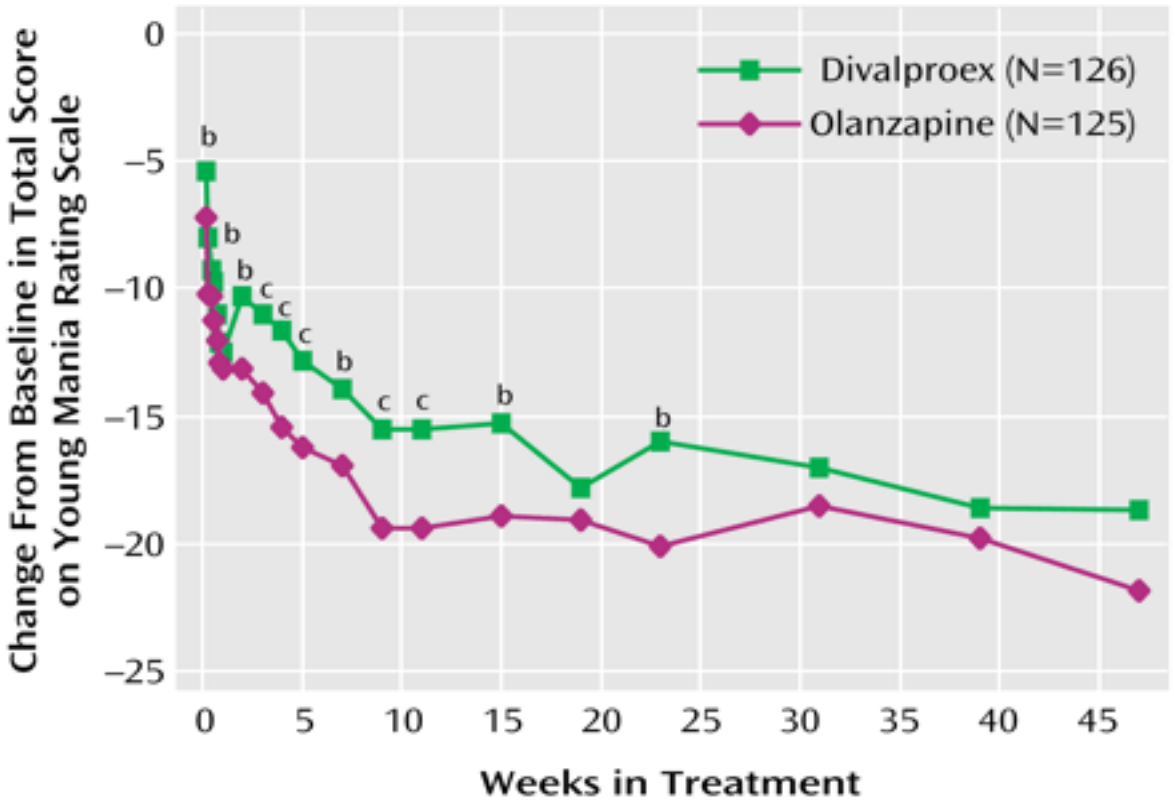
Academic Clinical Fellow in General Adult Psychiatry

Use of valproate in bipolar disorder (BAP, 2016)



- Valproate semisodium (Depakote) effective in acute mania
- Small studies in bipolar depression suggest it is could be effective (NB anxiolytic)

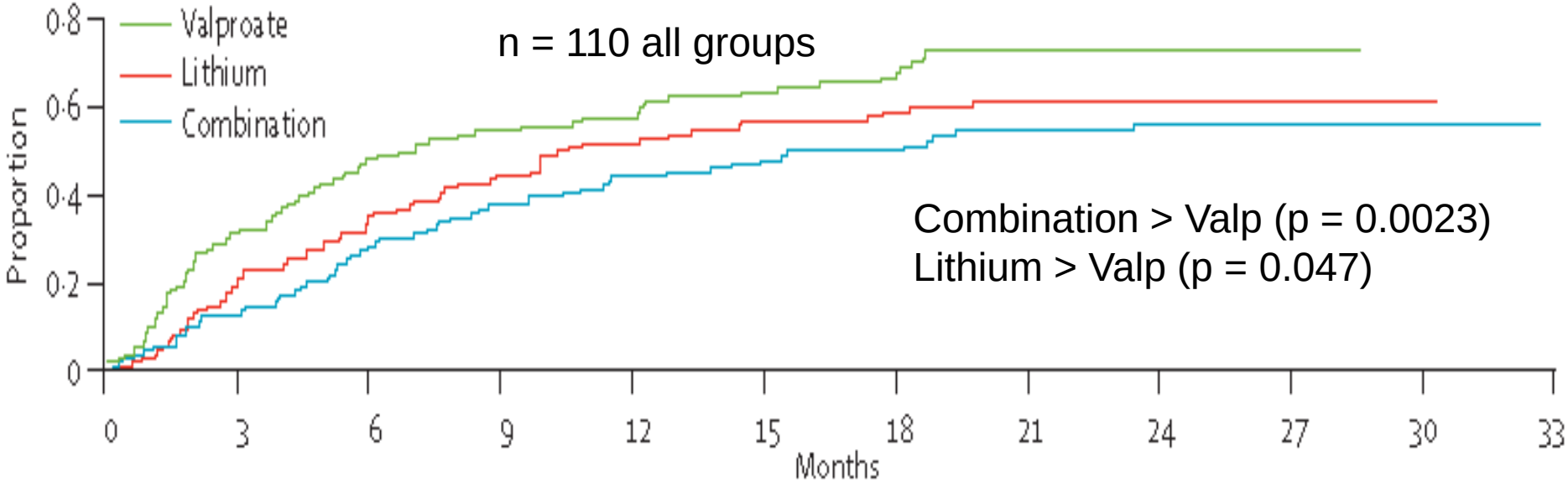
Divalproex versus Olanzapine (Tohen et al, 2003)



- Faster symptomatic relief from mania with olanzapine
- No **difference** in any measure of efficacy during maintenance period
- Relapse rates into depression and mania no different

BALANCE Trial (Geddes et al, 2009)

Primary outcome: Admission or treatment for new episode



Naturalistic evidence of efficacy of long term treatments in bipolar disorder

Table 2. Associations between different treatments and psychiatric hospitalization estimated using within-individual models (n=35,022).

	Hazard Ratio (95% CI)			
	All psychiatric hospitalizations	**Manic episodes**	**Depressive episodes**	**Mixed episodes**
Lithium	0.66* (0.62, 0.70)	0.56* (0.48, 0.65)	0.61* (0.53, 0.69)	0.56* (0.39, 0.79)
Valproate	0.73* (0.67, 0.79)	0.64* (0.53, 0.78)	0.73* (0.59, 0.89)	0.66* (0.44, 0.99)
Carbamazepine	0.92 (0.77, 1.10)	0.50* (0.29, 0.86)	0.98 (0.64, 1.48)	1.65 (0.59, 4.62)
Lamotrigine	0.78* (0.73, 0.84)	1.00 (0.78, 1.28)	0.73* (0.63, 0.84)	0.82 (0.53, 1.27)
Quetiapine	0.82* (0.76, 0.89)	0.73* (0.58, 0.93)	0.66* (0.54, 0.81)	0.92 (0.62, 1.39)
Olanzapine	0.77* (0.72, 0.83)	0.56* (0.46, 0.67)	0.80* (0.68, 0.93)	0.78 (0.52, 1.17)
Num. events	23383	4363	6637	973

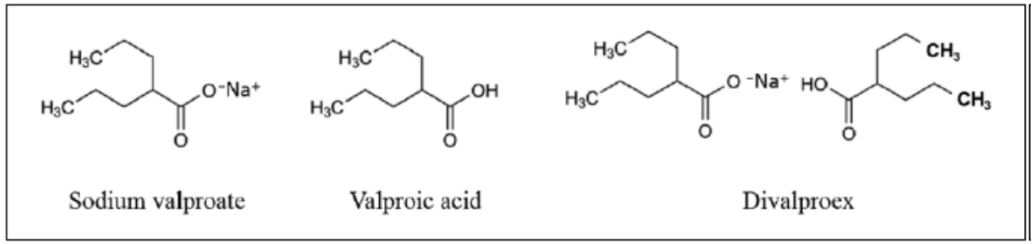
* 1 outside the confidence interval

All models adjusted for previous time spent in psychiatric inpatient care and age.

- 13,435 patients
- Li superior to everything except VPA
- VPA superior to CBZ

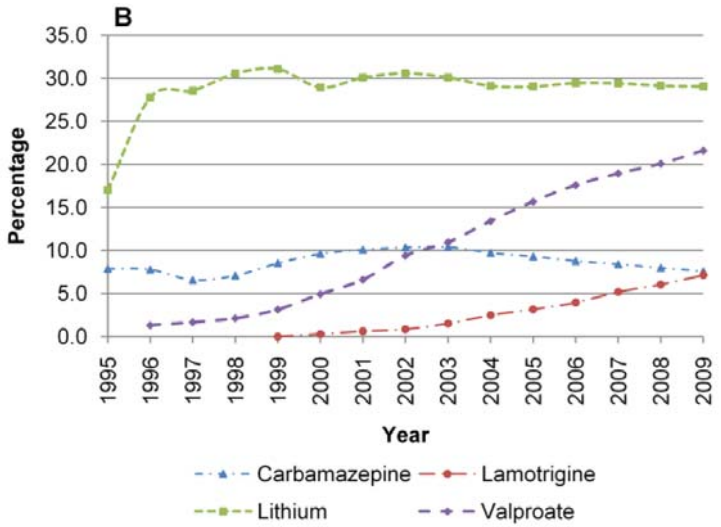
Joas et al. 2017 Brit J Psychiatry

Use of valproate in bipolar disorder (BAP, 2016)



- Valproate semisodium (Depakote) effective in acute mania
- Small studies in bipolar depression suggest it is could be effective (NB anxiolytic)
- Limited RCT in support of long term use
- Valproate monotherapy is less effective than lithium monotherapy
- Naturalistic data is the best evidence to support valproate
- Potential second line long term treatment after Lithium (BAP, 2016)

Use of valproate in women has increased



"In 1995 none of the women of childbearing age (18–45 years old) in our sample were prescribed valproate. By 2009, 233 out of the 682 women with two or more prescriptions that year were taking valproate (34.2%) and spent 35.6% of the year in treatment."

Hayes J, Prah P, Nazareth I, King M, Walters K, et al. (2011) Prescribing Trends in Bipolar Disorder: Cohort Study in the United Kingdom THIN Primary Care Database 1995–2009. PLOS ONE 6(12): e28725. https://doi.org/10.1371/journal.pone.0028725
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0028725

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Pre-conception counselling

- Adverse effects can occur before the pregnancy can be confirmed
- Higher incidence of PCO/S (1)
- Adverse spermatogenesis (2)
- AEDs small increase in miscarriage (16% vs 13%) (3)
- Advise to discontinue or switch
- Withdraw over 4 weeks and still use contraception (4)
- Switch to an antipsychotic (or possibly lithium or lamotrigine (5))
- Can prescribe if no other medications work and the patient is reliably taking a contraceptive

1. Hu et al., 2011; Svalheim et al., 2015
2. Reynolds-May et al., 2014
3. Bech et al, 2014
4. Goodwin et al., 2016
5. McAllister-Williams et al. 2017

Proportion of patients prescribed valproate who had information about adequate contraception and were informed of the risks that valproate would pose to an unborn baby (POMH, Paton et al 2018 in press)

Documented evidence regarding woman's childbearing potential or use of contraception	TNS N = 74	Trust 008 N = 2
No documented evidence of protection against pregnancy	48 (66%)	2 (100%)
Takes oral contraceptive	9 (12%)	0 (0%)
Patient has an IUD/coil fitted	4 (5%)	0 (0%)
Patient has had an injectable contraceptive or implant fitted	6 (8%)	0 (0%)
Other contraceptive method documented	6 (8%)	0 (0%)
Patient has undergone an oophorectomy/hysterectomy/endometrial ablation	1 (1%)	0 (0%)

Documented evidence of the following:	TNS N = 74	Trust 008 N = 2
A general discussion regarding side effects and benefits of the treatment	49 (66%)	1 (50%)
Discussion with the woman of the need for adequate contraception during valproate treatment	41 (55%)	1 (50%)
The woman was informed of the risks to the foetus when valproate is taken during pregnancy	37 (50%)	1 (50%)
The woman was informed of the implications for the longer-term cognitive development of the child when valproate is taken during pregnancy	18 (24%)	0 (0%)
The woman was given the MHRA leaflet that outlines the problems associated with valproate in pregnancy	6 (8%)	0 (0%)
None of the above	20 (27%)	1 (50%)

Guidance

Toolkit on the risks of valproate medicines in female patients

Information about the toolkit to ensure female patients are better informed about the risks of taking valproate medicines during pregnancy.

Published 8 February 2016
Last updated 13 September 2017 — see all updates
From: Medicines and Healthcare products Regulatory Agency

Documents

Guidance on using the valproate toolkit for those prescribing and dispensing valproate

PDF, 35.7KB, 2 pages

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Related content

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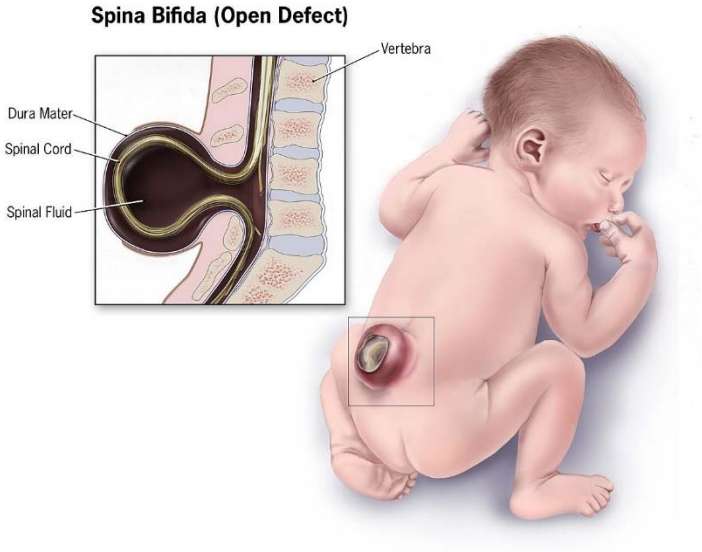
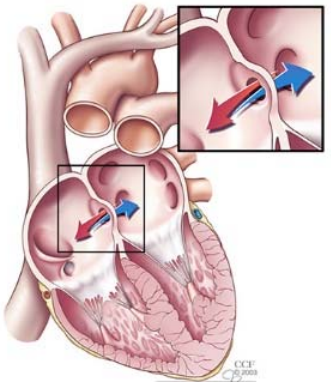
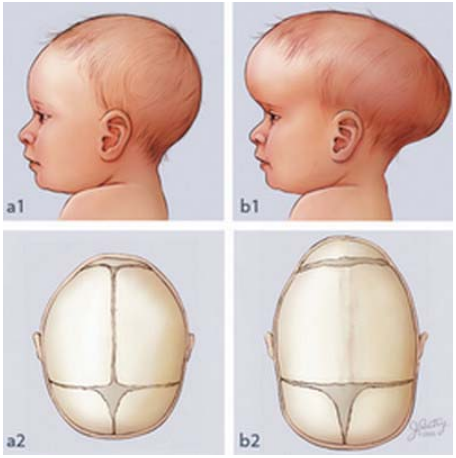
Teratogenicity







What is the risk of malformation? (Cochrane 2006)

Malformation	Epilepsy (Y/N)	No medication	Sodium valproate	Relative risk	Risk difference	
MCM	N	2.4%	9.6%	5.69	0.08	Significant
	Y	2.46%	8.5%	3.13	0.07	Significant
NTM	N	0.23%	1.4%	6.05	0.01	Non-sig
	Y	0.33%	2.8%	5.30	0.03	Significant
CM	N	0.46%	7.4%	16.4	0.07	Significant
	Y	0.33%	3.44%	4.85	0.03	Significant
OF/CFM	N	0.07%	1.4%	2.76	0.01	Non-sig
	Y	0.33%	3.01%	5.16	0.03	Significant
SLM	N	0.23%	4.23%	16.48	0.04	Non-sig
	Y	0.66%	2.37%	2.57	0.02	Non-sig

Dose-response relationship

UK Register N=1220 exposed to sodium valproate

- 5% <600 mg/day
- 10.4% >1000 mg/day

Neonatal effects

Kallen et al (2012)	**Pennell et al (2012) - NEAD Study**
• Swedish Medical Register • 862 early exposures • 212 late exposures • Pre-term birth (OR = 1.61, 95% CI 1.16-2.98) • Morbidity (OR = 1.99, 95% CI 1.43-2.78)	• Prospective observational study • N = 309 (?SV) • Odds ratio higher for SGA and reduced APGAR scores at 1 minute • Possible microcephaly

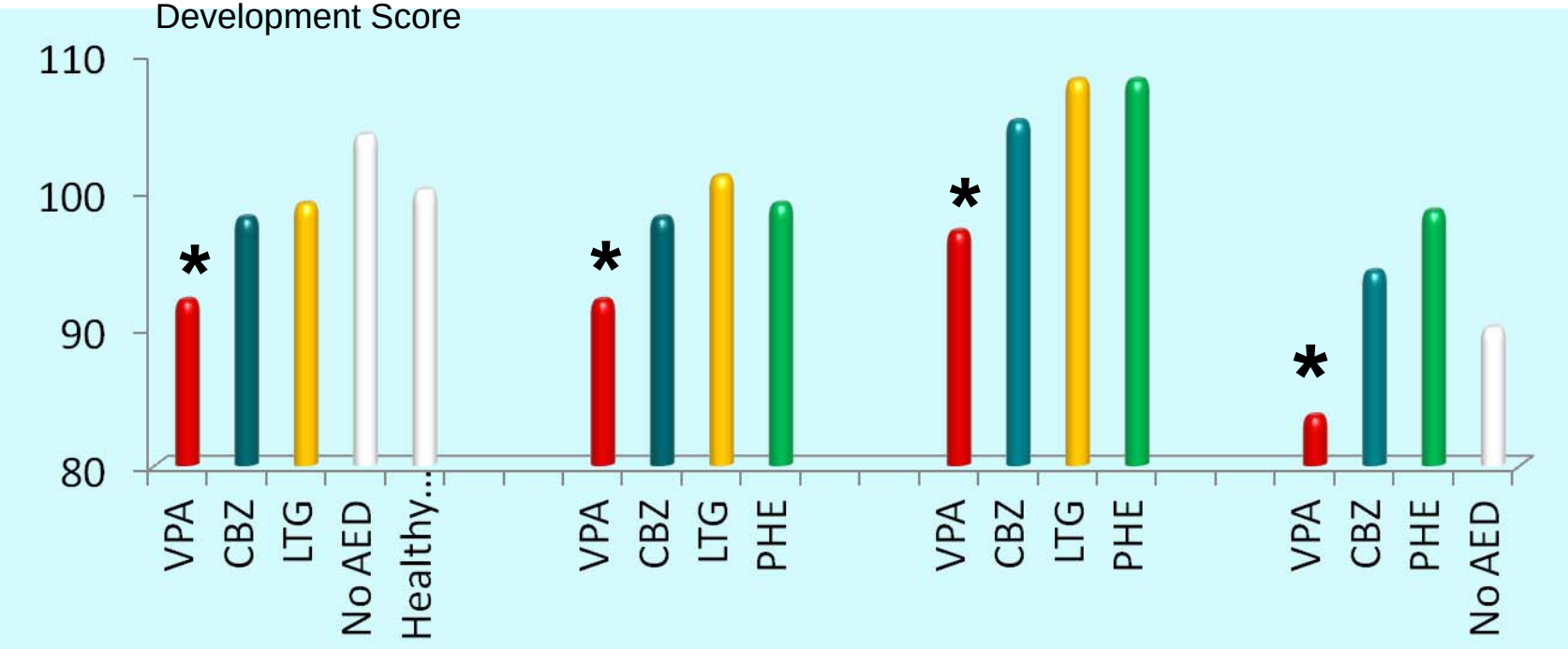
Neurodevelopmental Outcomes

Study 1:
4 months– 2 years
Griffiths Mental Development Score

Study 2:
Age 3
IQ (Bayley Scales)

Study 3
Age 6
Mean IQ (Wechsler)

Study 4:
Age 6-16 years
Verbal IQ (Wechsler)



*** = significant difference to other groups**

1. Bromley et al, Epilepsia 2010; 51(10): 2058-2065
2. Meador *et al*, N Engl J Med 2009; 360(16):1597-605.
3. Adab *et al*, J Neurol Neurosurg Psychiatry 2004; 75(11):1575-83
4. Meador et al, The Lancet 2013 http://dx.doi.org/10.1016/S1474-4422(12)70323-X

Advice for pregnant women taking valproate

- (Almost!) Always stop (and probably switch e.g. to an antipsychotic)
  - If not switching, change to slow release twice daily (+) and lowest dose possible
- No evidence that folic acid prevents valproate NTDs
  - Vajda et al (2003): retrospective data from Australian register, compared children with and without birth defects, 2/3 in each group took pre-conception folic acid
  - Folic acid may reduce background risk, or higher lesions that are more folic acid responsive.
  - Folic acid 5mg for 3 months pre- and post-conception
- AFP screening for NTDs + US scan 16-18 weeks
- Do not breastfeed

Future directions

- MONEAD (Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs) Study (N=565), finished recruitment

  - How many minor malformations are caused by valproate?
  - Is sodium valproate associated with less or more severe spina bifida?
  - Does the research in sodium valproate for epilepsy apply to women with bipolar disorder?
  - Sodium valproate vs valproate semisodium?
  - How much of the increased risk is caused by other confounding factors?

- **Could there be a ban?**