



Valproic acid in pregnancy and development

January 31, 2012



Overview

- Case presentation—Anna
- Pregnancy and Depakote—Anna
- Valproic acid in detail—Mandy
- Dysmorphic features—Mandy
- Developmental delay—Veronica
- Resources—Veronica

Our Case

- 27 month old boy ex-full term
- Chief concern: Speech
- HPI
 - Starting babbling around 8 months of age
 - First word at 14-18 months → “Dad”
 - First evaluation in June 2011 by speech therapy → expressive speech problem
 - Went to ST once/week to work on expressive speech
 - Progress report in Nov 2011: No improvement. On eval found expressive AND receptive speech problem.
 - Parents said currently could only say “clap” and “bye”

PMH

- Birth
 - Born to G2P2 39-year old mom with Bipolar Type II disorder. Mother taking **1,000 mg Depakote** for bipolar as well as folic acid.
 - Induced vaginal delivery at 40 wks, no complications.
 - Jaundice soon after birth requiring phototherapy x1-2 d.
- Born with cleft left thumb that was repaired July 2011.
- Normal hearing test at birth and Nov 2011.
- Meds: hydrocortisone for eczema.
- FH: Bipolar disorder in mother, uncle and maternal grandmother. Cousin had speech delay and ?IQ. Aunt had speech delay. Father's side—anxiety.

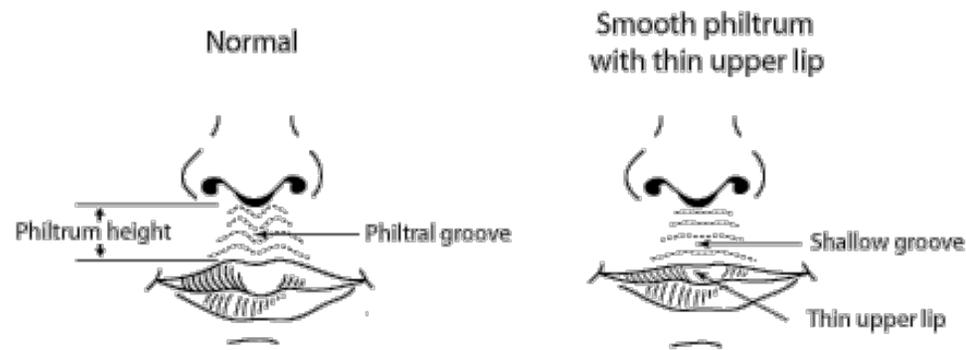
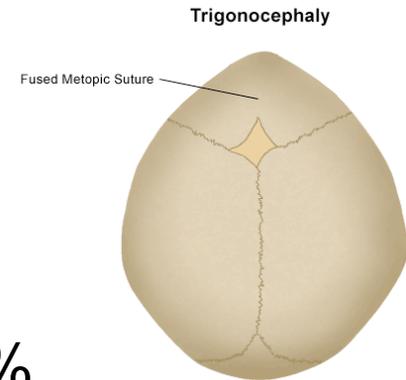


Developmental hx

- Sat independently at 4-5 mo
- Walked at 13 mo
- Waved bye-bye at 18 mo
- Pointed at 20 mo
- Does not use two-word commands, pretend or imagined play or toilet-trained.

Physical Exam

- General: interactive, sweet
- Growth: ht 55%, wt 76%, wt:ht 85%, HC 60%
- Dysmorphic features: mild trigonocephaly, short anteverted nose, mild smooth philtrum.
- Neuro: CNs intact. Facial and shoulder symmetry. Reflexes 2+ bilateral. Mild LOW tone upper and lower ext. Gait normal. Needed assistance walking up/down stairs.



Assessment

- CLAMS score: 52 DQ
- CAT score: 83 DQ
- Parent and caretaker evaluation forms: borderline and significant pervasive dev problems
- SOCIAL: initially interactive, then shut down during CAPUTE evaluation.
- Overall: Speech and language delay of reception and expressive type. Also inconsistent social interactive, suggestive of some autistic features. Could be linked to Depakote use in pregnancy...

Valproic Acid and Pregnancy

- Data regarding fetal effects of VPA derived primarily from studies of women with seizures. Whether the underlying pathology of epilepsy contributes to the teratogenic effect on the fetus is unclear.
- In pregnancy, it is not uncommon for a woman with bipolar disorder to present for treatment when she is past 28 days and thus beyond the period when neural tube closure occurs.
- Even when the mother presents before preg, the high relapse rates for women with bipolar disorder after medication discontinuation may argue for medication continuation.

Valproic Acid has worse outcomes

- More adverse outcomes (congenital malformation, death) were observed in pregnancies with in utero valproate exposure vs the other antiepileptic drugs (AEDs). These results combined with several recent studies provide strong evidence that valproate poses the highest risk to the fetus.
- For women who fail other AEDs and require valproate, the dose should be limited if possible.
- Valproic acid crosses the placenta and is present in a higher concentration in the fetus than in the mother.
- **Dose-dependent of congenital malformations for VPA
- The rate of serious adverse outcomes was 24.2% for VPA when doses were at or above the median first trimester dose (i.e., 900 mg/day) and was 9.1% for doses below the median. The mean (range) dose for those with serious adverse outcomes was 1,268 mg/day (200 to 2,750 mg/day).

Risk categories for VA

- Pregnancy Risk Category (ACOG): D (possible evid for risk)
- AAP Rating: compatible.
- Lactation risk category: L2 (safer). No adverse effects have been noted of children BF from a mother taking VPA.

Practical tips in pregnancy

- If treatment with VPA cannot be avoided, the least effective dose be used and the division of the daily dose into 3 or 4 equal doses administered throughout the day.
- Diet should be fortified with an adequate amount of folate prior and throughout conception.
- Fetuses exposed to VPA should undergo detailed prenatal US evaluation to detect any limb or systemic abnormalities.
- Because maternal serum alpha fetoprotein may not be elevated in all cases of neural tube defects in fetuses exposed to VPA, the direct use of amniocentesis and fetal ultrasound examinations are recommended.

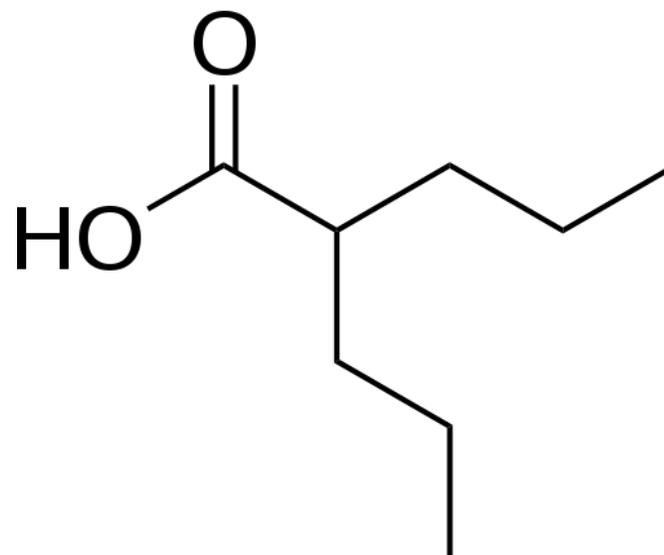
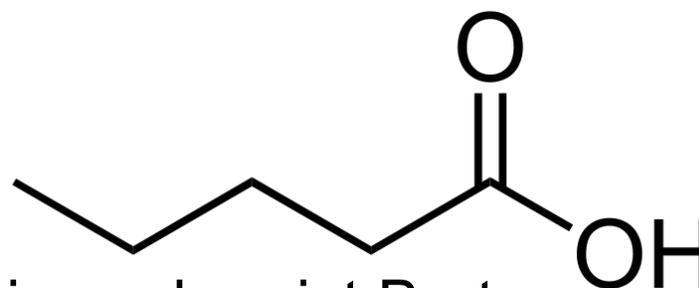


If VP used in pregnancy...

- Recognize different formulations
- Know what effects to look for

History

- First synthesized in 1882 by American chemist Burton
- Analogue of valeric acid found in the valerian plant
- First used as an organic solvent
- Anticonvulsant properties discovered by French chemist Eymard in 1962



Valerian Root

- Herbal supplement sold in the U.S.
- According to NCCAM, used for sedative and anxiolytic effects
- Very limited animal and human data do not allow a conclusion as to the safety of valerian during pregnancy.



Valproic Acid

Brand Names:

- Depacon®
- Depakene®
- Depakote®
- Depakote® ER
- Depakote® Sprinkle
- Stavzor™



Uses:

- Anticonvulsant
- Mania/Bipolar disorder
- Migraine prophylaxis
- Diabetic neuropathy

Adverse Reactions:

- CNS: Headache ($\leq 31\%$), somnolence ($\leq 30\%$), dizziness (12% to 25%), insomnia (1% to 15%), nervousness (1% to 11%), pain (1% to 11%)
- DERM: Alopecia (1% to 24%)
- GI: Nausea (15% to 48%), vomiting (7% to 27%), diarrhea (7% to 23%), abdominal pain (7% to 23%), anorexia (1% to 12%)
- HEME: Thrombocytopenia (1% to 24%; dose related)
- MSK/Neuro: Tremor ($\leq 57\%$), weakness (6% to 27%)
- Ocular: Diplopia (>1% to 16%), amblyopia/blurred vision ($\leq 12\%$)
- Miscellaneous: flu-like syndrome (12%)
- Black Box Warning: Risk of fulminant hepatic failure increased in children < 2 y/o. Life-threatening pancreatitis reported in adults <1%.

Fetal Valproate Syndrome

- Caused by prenatal exposure to valproic acid
- Highest risk during the first trimester
- Characterized by a cluster of distinctive facial features, major and minor anomalies, and CNS dysfunction/DD
- Mechanism of teratogenicity remains unclear but hypothesized to interfere with folate cycle

FVS: facial features

- trigonocephaly
- hypertelorism
- small ears, posterior
- small broad nose
- long or flat philtrum
- micro or retrognathia
- small mouth.

7-month-old girl with fetal valproate syndrome

Smith's Recognizable Patterns of Human Malformation
5th edition 1997

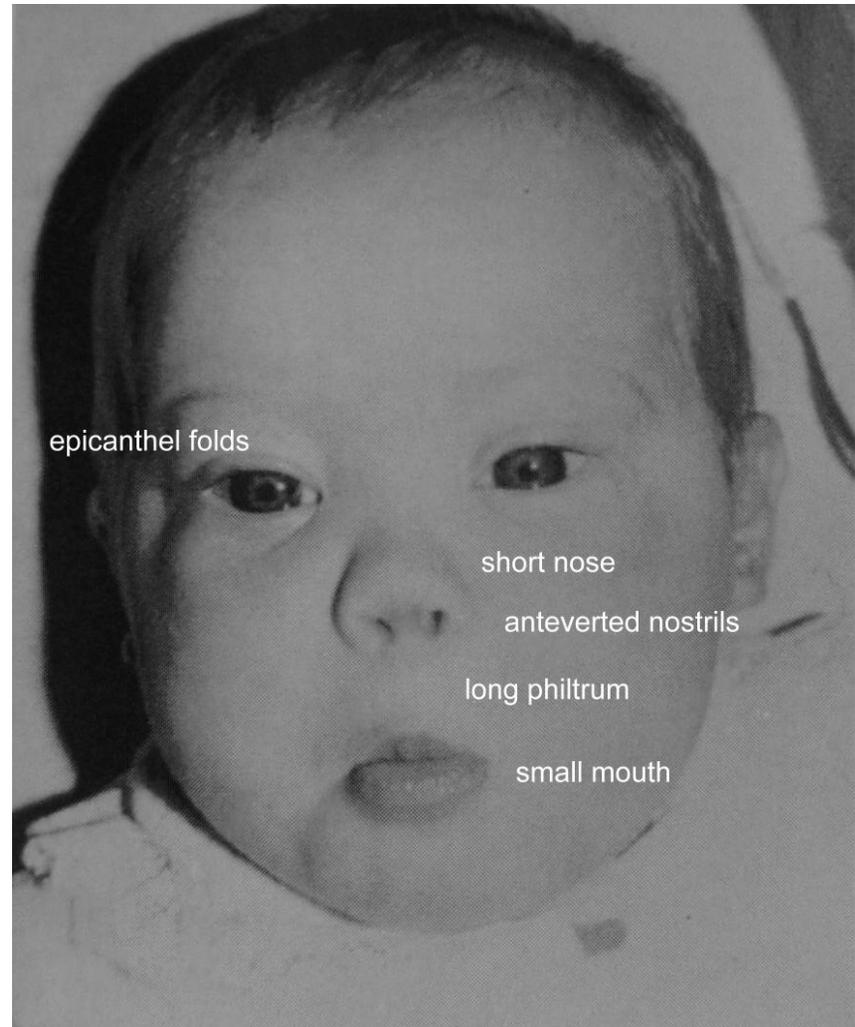


TABLE III. Fetal Valproate Syndrome
Cardiovascular Malformations

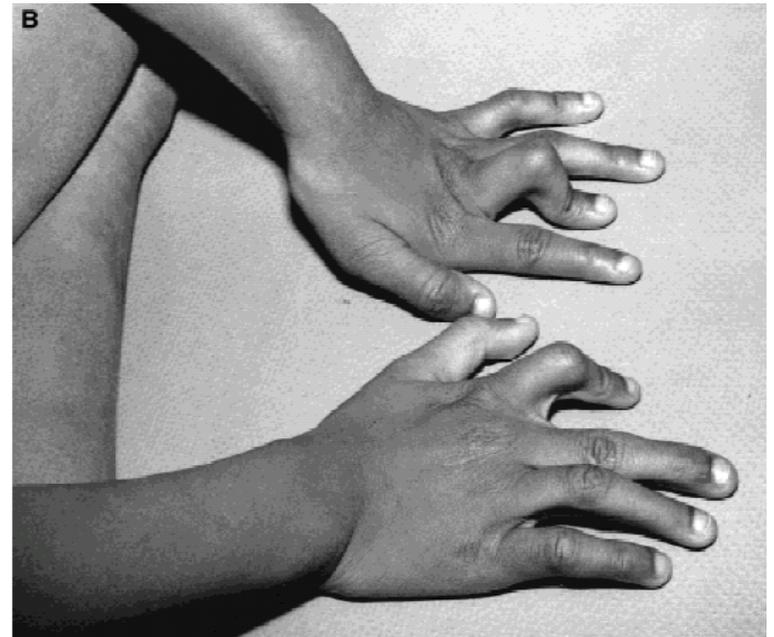
Reference	Cardiovascular abnormalities
Dalens, 1980	Levocardia, partial right bundle branch block
Clay et al., 1981	VSD
Bailey et al., 1981	Aortic stenosis
DiLiberti et al., 1984 (Case 6)	Aortic stenosis
Jager-Roman et al., 1986 (Case 1)	Lesion not specified
Jager-Roman et al., 1986 (Case 13)	PDA
Winter et al., 1987 (Case 2)	VSD
Winter et al., 1987 (Case 3)	Pulmonic stenosis
Ardinger et al., 1988 (Case 3)	Lesion not specified
Ardinger et al., 1988 (Case 4)	Lesion not specified
Huot et al., 1987 (Case 2)	Abnormalities of coronary sinus, anomalous left Superior vena cava
Janas et al., 1998 (Case 3)	Coarctation of the aorta, transposition of the great vessels, VSD
Thisted and Ebbegen, 1993 (Case 4)	ASD, VSD
Thisted and Ebbegen, 1993 (Case 10)	Pulmonary stenosis
Thisted and Ebbegen, 1993 (Case 11)	Tetralogy of fallot
Hockey et al., 1996	ASD, PDA
Mo and Ladusans, 1998 (cases 1 & 2)	Anomalous right pulmonary artery, tricuspid regurgitation, abnormal origin of right pulmonary artery, dysplastic pulmonary valve

Kozma, AJ. American
Journal of Medical Genetics.
2001.

FVS: limb anomalies

TABLE II. Fetal Valproate Syndrome
Musculoskeletal Abnormalities

	Case 1	Case 2	Total cases (70)	%
Abdominal wall defects	-	-	10/70	14
Fingers abnormalities/contractures	+	+	25/70	36
Foot abnormalities	+	+	21/70	30
Thumb abnormalities	-	-	12/70	17
Radial defects	-	-	11/70	16
Nails abnormalities	-	-	7/70	10
Thoracic cage abnormalities	-	-	5/70	7
Large joint abnormalities	+	-	4/70	6



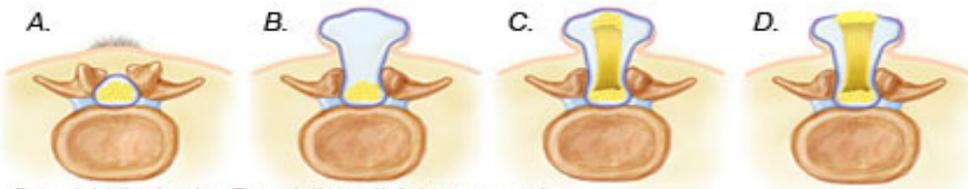
FVS: neural tube defects

- Estimated to be around 1-2%
- General population risk estimated to be 0.14% to 0.2%
- Advised to take folic acid supplementation if on VA

Cyst on baby's back
from spina bifida



- A. Spina bifida occulta
- B. Spina bifida with meningocele
- C. Spina bifida with meningomyelocele
- D. Spina bifida with myeloschisis





FVS: CNS/cognitive

- Growth retardation
- Hypotonia
- MR
- Seizures
- Developmental deficits
- Anencephaly

Long term effects and AEDs

- Teratogenicity: Maternal epilepsy itself or AED?
- AED and malformations, 4-6% risk
 - valproate
 - polypharmacy and higher AED dose
 - timing and dose of exposure
- AED exposure in utero may be associated with impaired cognitive development
- Evidence for this association is strongest with valproate

Valproate and IQ

- Meador study, NEJM 2009
- IQ lower for valproate compared to lamotrigine, phenytoin, carbamazepine at 3 years age
- IQ score and valproate exposure: dose related relationship

Valproate versus carbamazepine

- Prospective study of 172 infants
- Mean age of 15 months
- valproate: lower mental and motor developmental quotients compared with carbamazepine

Valproate and language

- Lower than mean average language test scores on blinded assessments
- Lower verbal intelligence associated with exposure to valproate and AED polytherapy but not to carbamazepine monotherapy

Valproate and Autism

- Liverpool and Manchester Neurodevelopment group prospective study
- 6.3 percent of children exposed to valproate in utero developed autism spectrum disorder
- 10-fold higher rate than in the general population

National Guidelines

Is cognition reduced in children of WWE exposed to AEDs in utero?

Recommendations

- Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE
- Avoiding valproate, phenytoin and phenobarbital in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes
- Monotherapy should be considered in place of polytherapy, if possible, during pregnancy to reduce the risk of poor cognitive outcomes

National Guidelines

Is exposure to a specific AED in utero associated with poor cognitive outcomes compared to other AEDs?

- For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine or phenytoin to reduce the risk of poor cognitive outcome

Resource for Families

- Organisation For Anti-Convulsant Syndrome
 - PO Box 772
 - Pilling
 - Preston, Intl PR3 6WW UK
 - Phone #: 012-53 -790022
 - 800 #: N/A
 - e-mail: janet.oacs@o2.co.uk or tegs78@ntlworld.com
 - Home page: <http://www.oacs-uk.co.uk/>