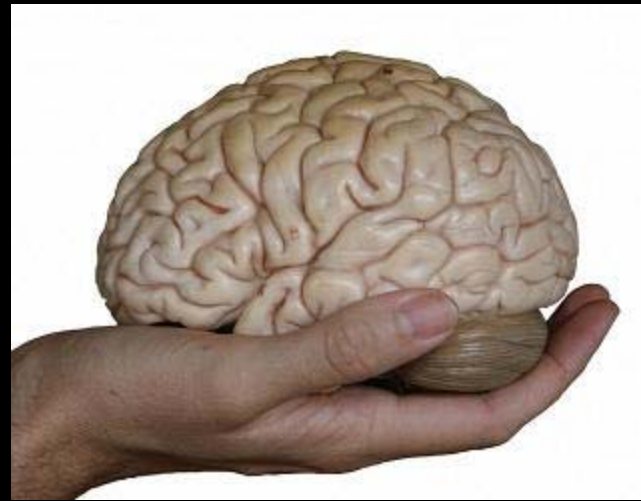


Efficacy of Anti-Epileptic Medications for Angelman Syndrome

T. J. Bichell, V. Kimonis,
E. Sanborn, C. Bacino, A.
Beaudet, L. Bird, M. Nespeca

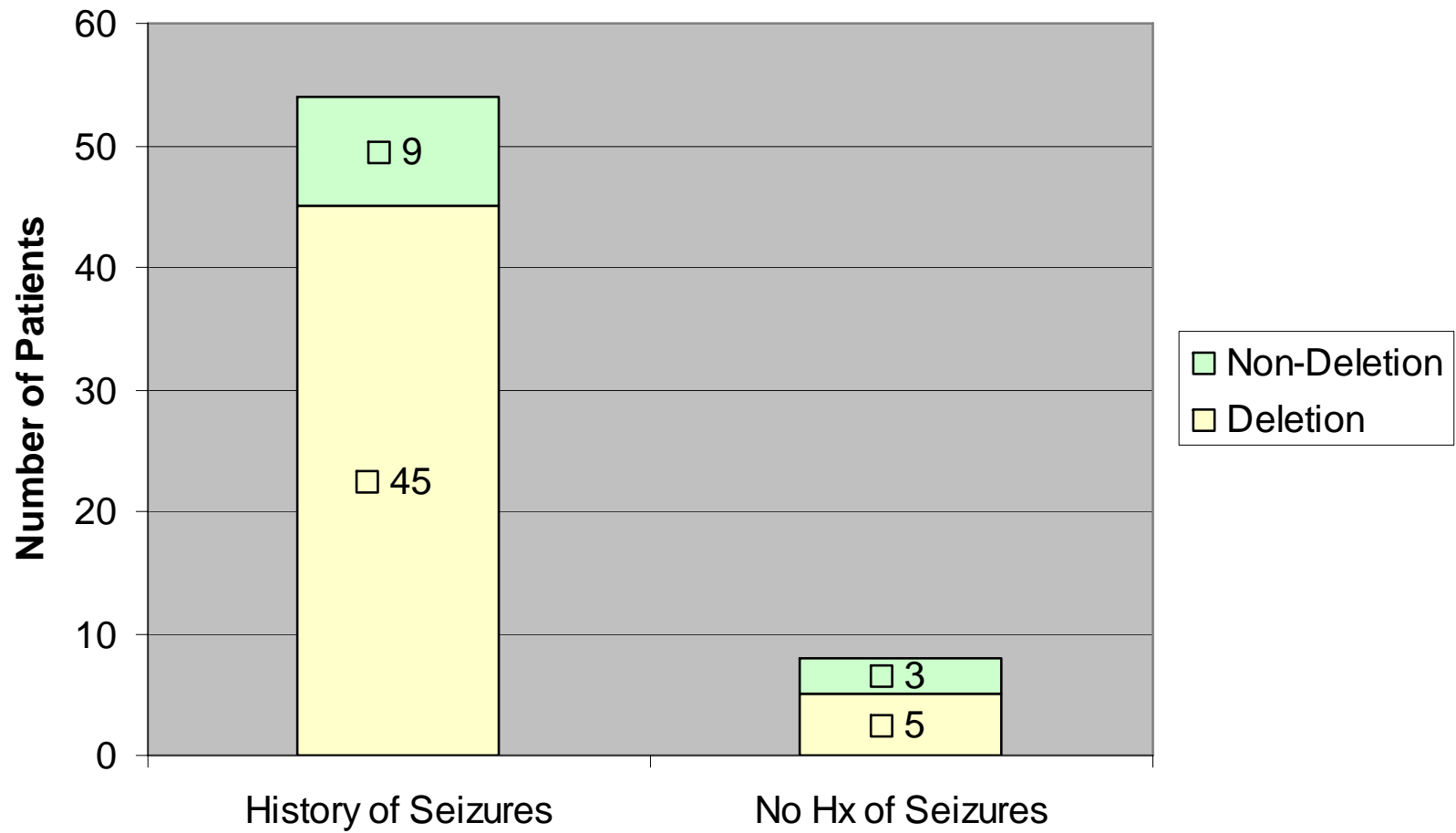
-
- *The world is full of obvious things which nobody by any chance ever observes.”*
--Sherlock Holmes



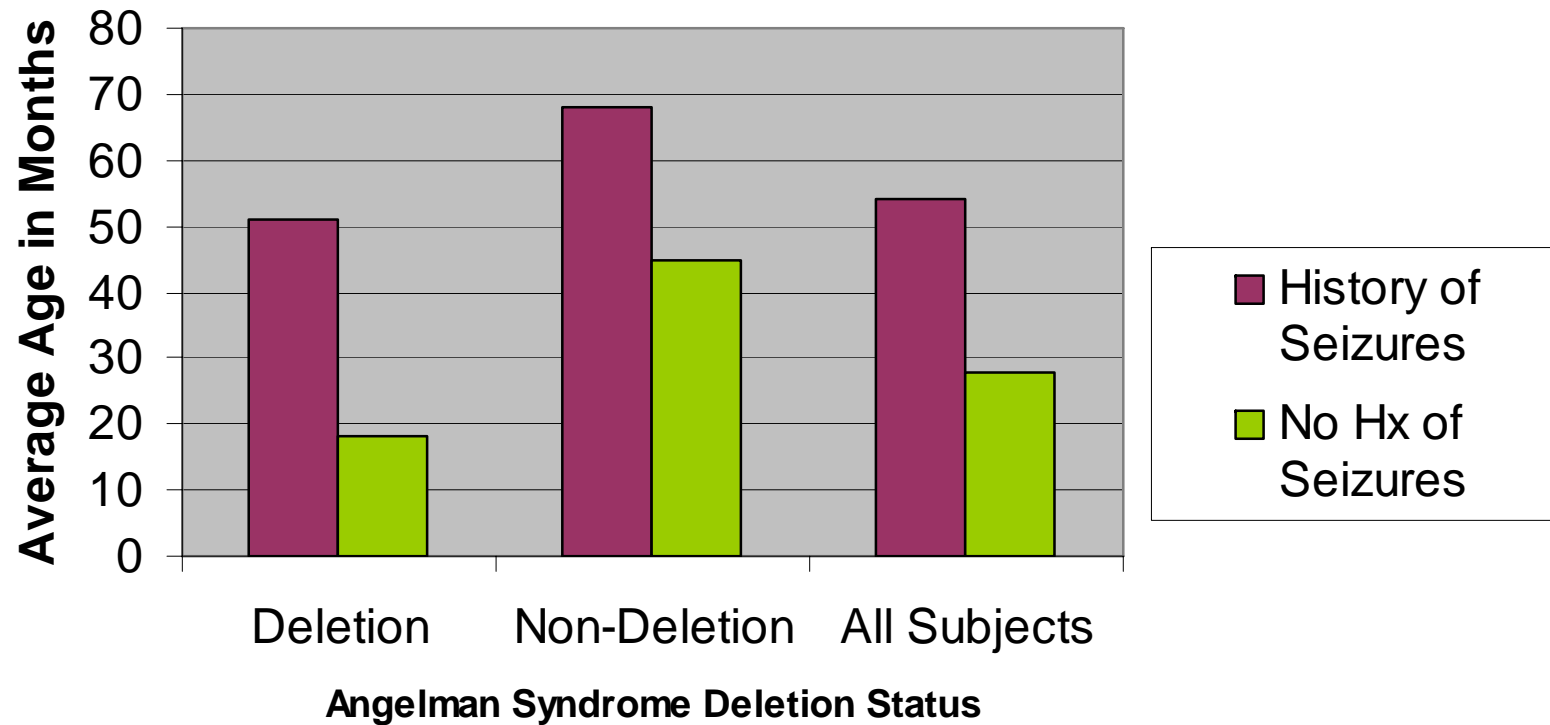
Folic Acid/Betaine Study

- Conducted from 2001-2006
- N = 62
- Four visits
- Parent Interviews
- Medical Histories
- Physical Examinations – Geneticists, Neurologists
- EEG's

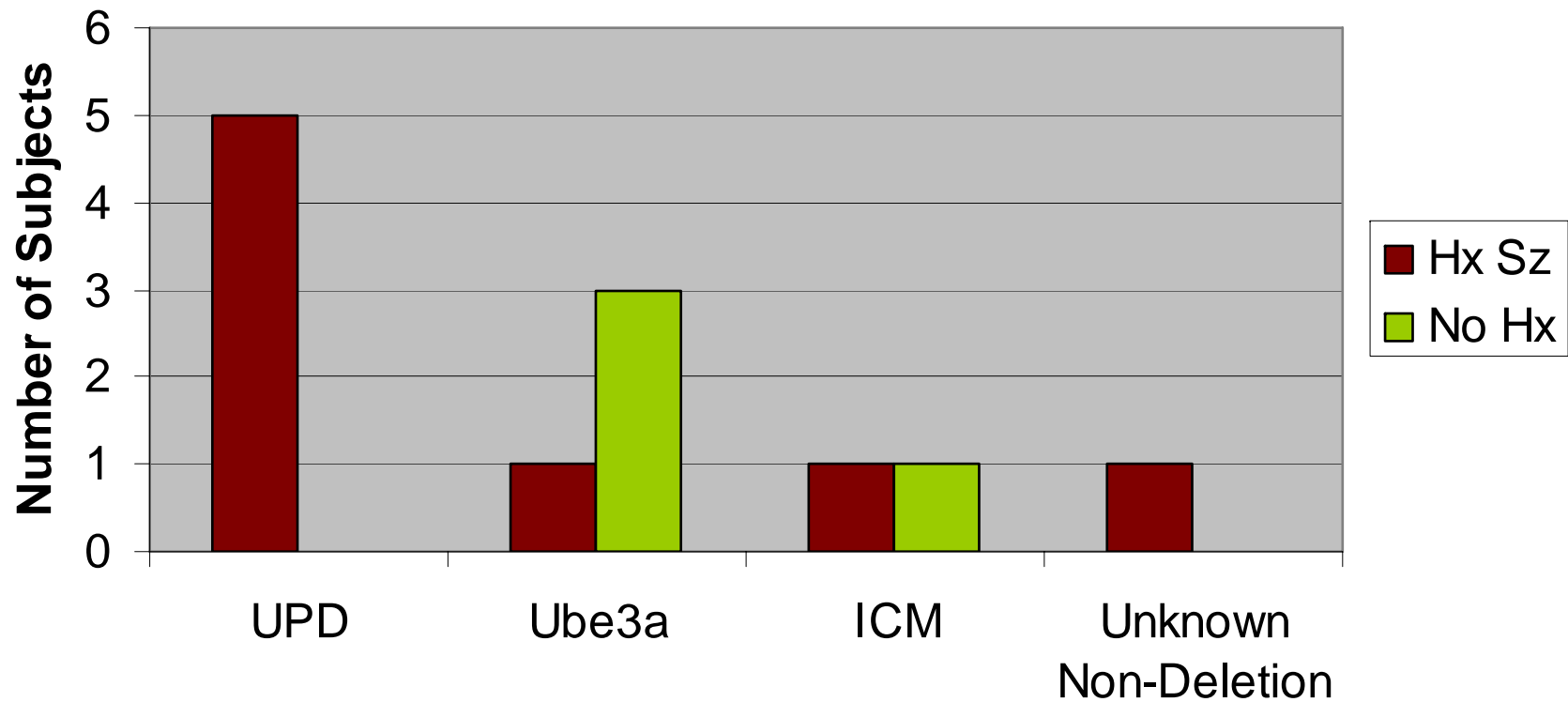
History of Seizures and Deletion Status



Age at Entry into Folic Acid/Betaine Study

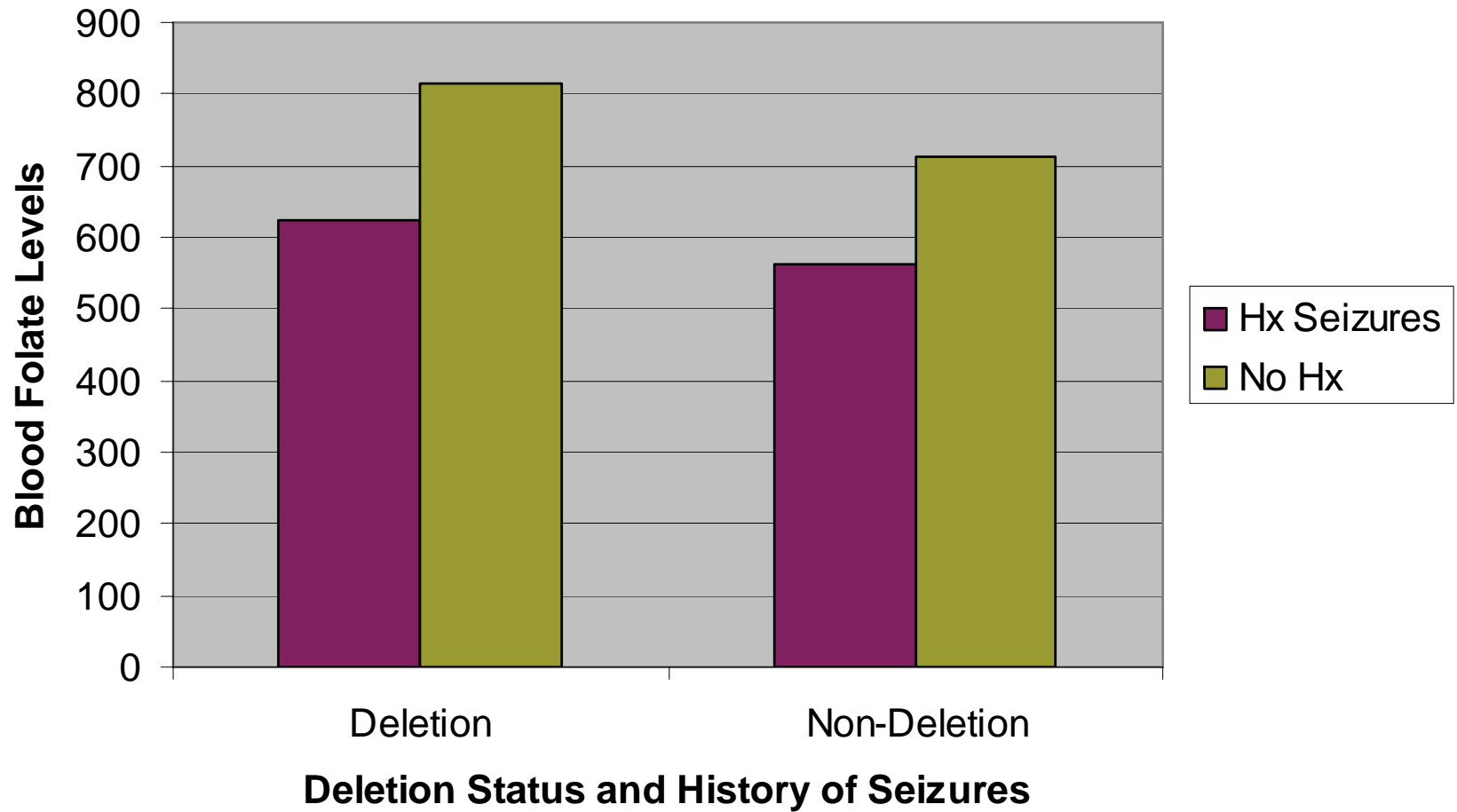


History of Seizures in Non-Deletion Subjects

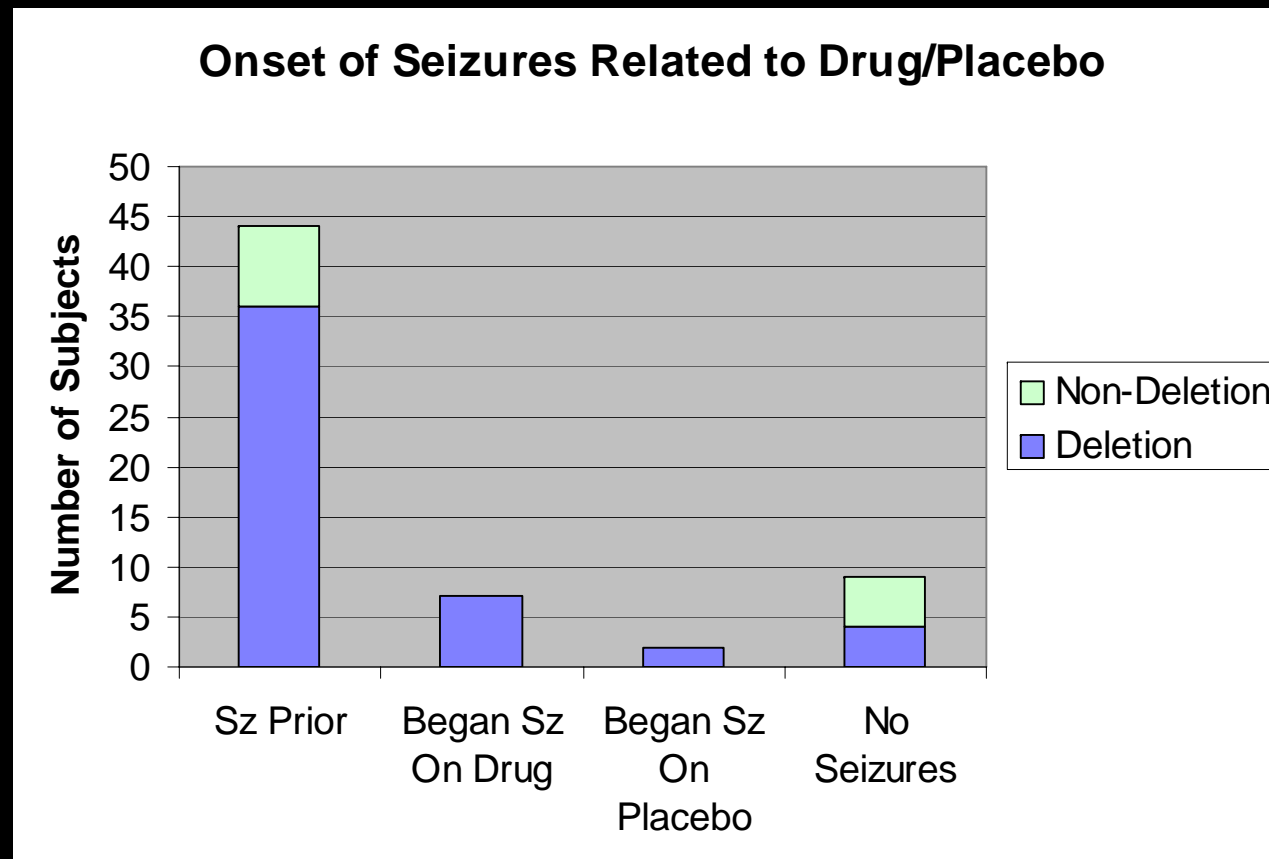


Genetic Diagnosis of Angelman Syndrome

Pre-Study Folate Levels



Effect of Study Medicine



Subjects without Seizure History

- 9 of 62 subjects, younger at entry to study
- Pre-Study blood folate levels higher
- 4 are Ube3a, of which 3 are on Keppra
- 1 is ICM
- 2 are Class 1 Deletion, 1 on Depakote
- 3 are Class 2 Deletion

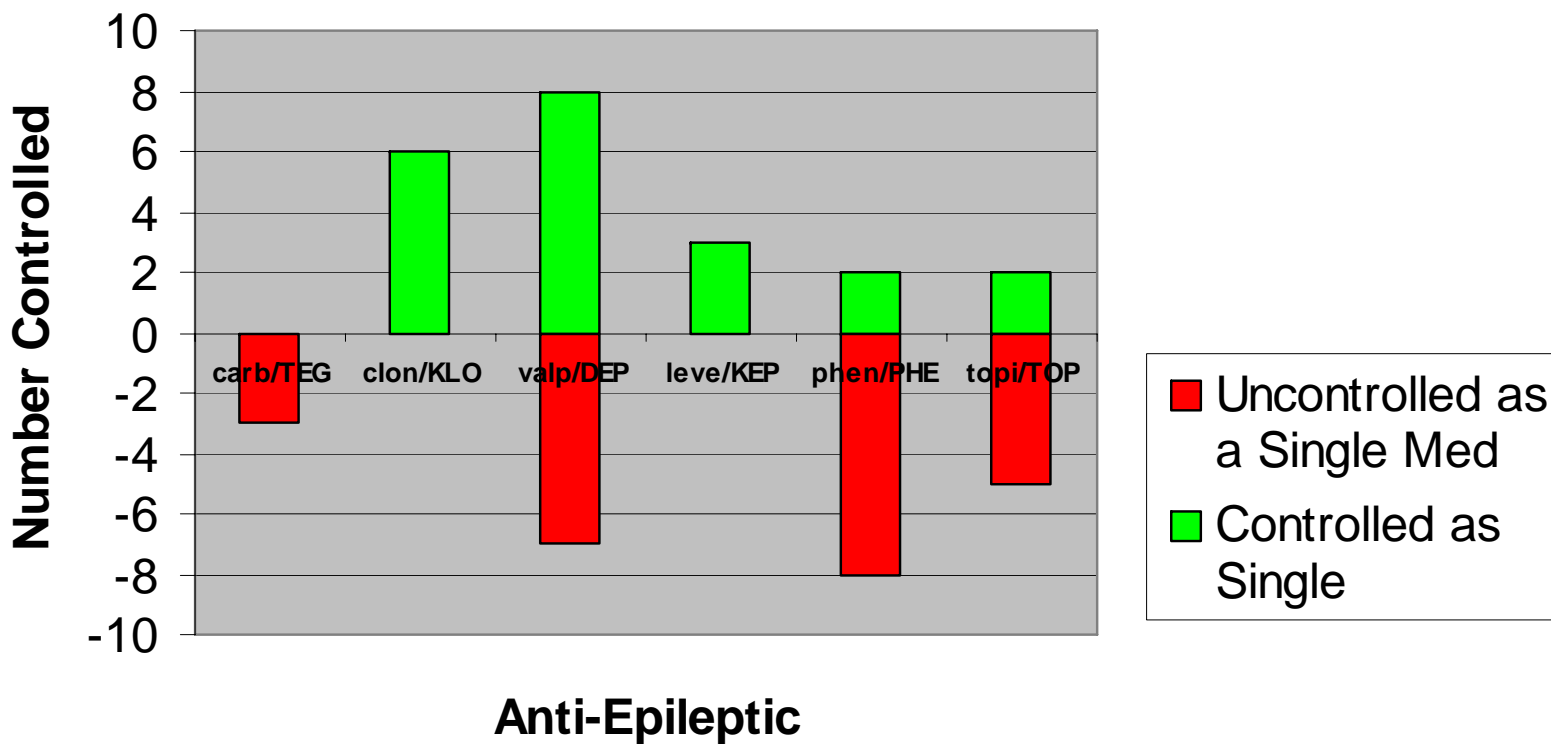
Definition of Effectiveness

- Seizure-free at time of follow-up interview for at least 6 months.
- Many had been seizure-free for much longer than 6 months
- Note: some had visible absence seizures but parents had reported them to be seizure-free

Anti-Epileptics Used Singly

- Depakote or Depakene/divalproex sodium or valproate sodium 8/15 = 53%
- Gabitril/tiagabine hydrochloride 0/1 = 0%
- Keppra/levetiracetam 3/3 = 100%
- Klonopin/clonazepam 6/6 = 100%
- Phenobarb/phenobarbital 2/10 = 20%
- Tegretol/carbamazepine 0/3 = 0%
- Topamax/topiramate 2/7 = 29%
- Tranxene/clorazepate dipotassium 1/1 = 100%

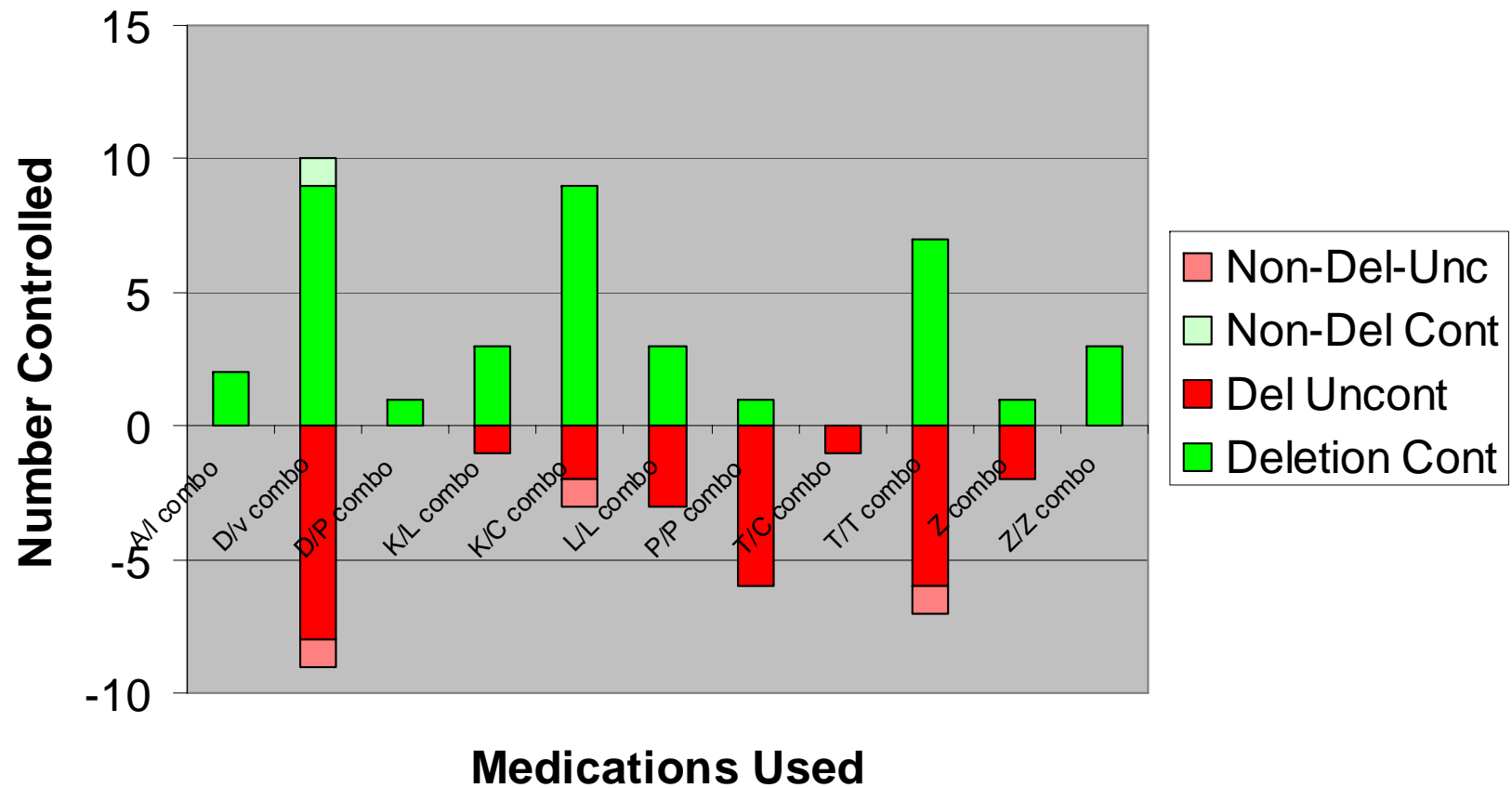
Effectiveness of Anti-Epileptics Used as a Single Drug in Angelman Syndrome



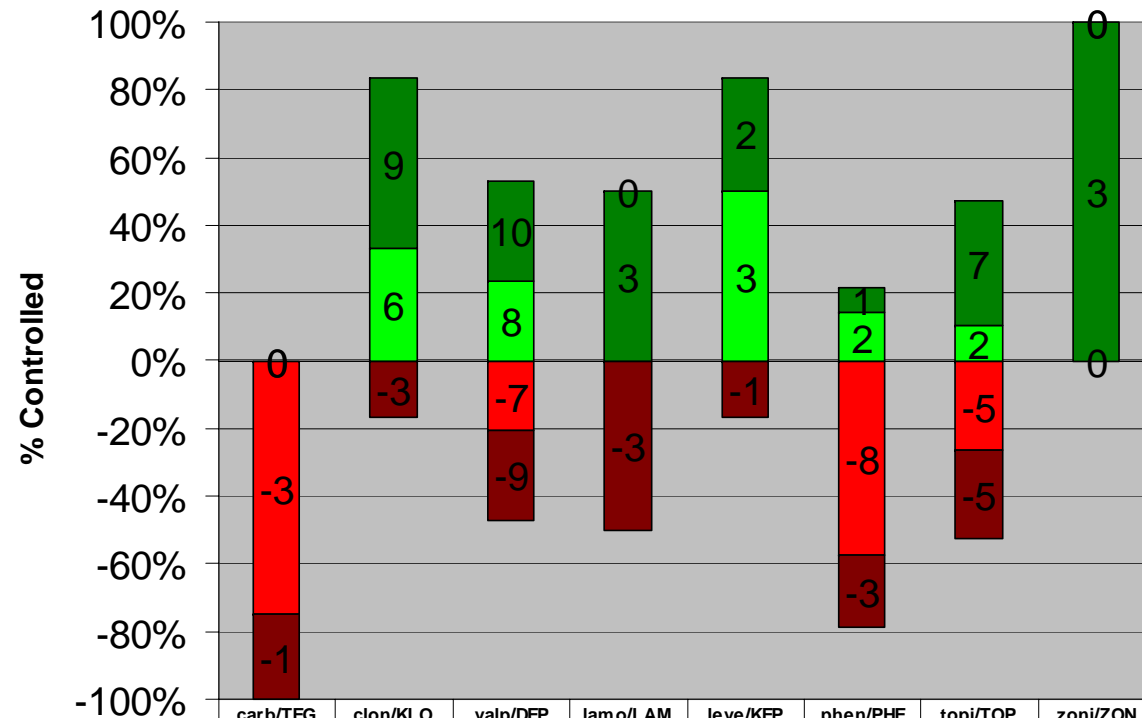
Anti-Epileptics Used in Combinations

- Ativan/lorazepam 2/2 100%
- Depakote or Depakene/divalproex sodium or valproate sodium 10/19 53%
- Dilantin/phenytoin 1/1 100%
- Kepra/levetiracetam 2/3 66%
- Klonopin/clonazepam 9/12 75%
- Lamictal/lamotrigine 3/6 50%
- Phenobarb/phenobarbital 1/4 25%
- Tegretol/carbamazepine 0/1 0%
- Topamax/topiramate 7/12 58%
- Zarontin/ethosuximide 1/3 30%
- Zonigran/zonisamide 3/3 100%

Effectiveness of Anti-Epileptics Used in Combination for Angelman Syndrome



Effectiveness of Anti-Epileptics in Angelman Syndrome (used in 3 or more patients)



	carb/TEG	clon/KLO	valp/DEP	lamo/LAM	leve/KEP	phen/PHE	topi/TOP	zoni/ZON
■ Uncontrolled in Combination	-1	-3	-9	-3	-1	-3	-5	0
■ Uncontrolled as Single	-3		-7	0		-8	-5	0
■ Controlled in Combination	0	9	10	3	2	1	7	3
■ Controlled as Single	0	6	8		3	2	2	0

Anti-Epileptic Used

Prior Published Studies

of Anti-Epileptics for Angelman Syndrome

- Viani et al, J. Child Neurology 1995 n=18
 - “in all of our patients isolated seizures and myoclonic status epilepticus were controlled by sodium valproate or combined with clobazam”...“seizures were increased by carbamazepine”
- **Ruggieri, M. Arch Dis Child 1998 n=78**
 - Clonazepam and lamotrigene best seizure control and least side effects, valproate next best. Carbamazepine worst, with vigabatrin and phenobarbitol almost as bad.
- Ostergaard, J. Dev Med Child Neurology 2001, n=20
 - Benzodiazepines, valproate work well, while oxcarbazepine, carbamazepine, vigabatrin often worsen seizures.

Ruggieri, 1998:
Parent Questionnaire Study: N=78

Drug	#pts	#Sz	SzSeverity	Alertness	Behavior
VPA	45	+22	+15	-2	-4
CBZ	22	-14	-13	-13	-9
PB	5	0	0	-1	-2
PHT	5	+1	-2	0	-1
ESM	6	-1	0	-2	-3
LTG	13	+12	+7	+4	+5
VGB	9	-3	-3	-8	-3
CLB	5	+2	+2	+4	+1
CLZ	23	+17	+19	+6	+3
NTZ	4	+4	+4	+3	+2

Prior Published Studies

of Anti-Epileptics for Angelman Syndrome

- Nolt, D. Am J Health Syst Pharm 2003, N = 85
 - Clobazam and zonisamide best for sz and behavior but few subjects, Clonazepam and valproate next. Carbamazepine worst for sz and behavior.
- Galvan-Manso, M. Epileptic Disorders 2005
 - Clonazepam 100% positive response, valproate 80% controlled, phenobarb only 30% controlled. Carbamazepine and vigabatrin worst
- Valente M. et al, Arch Neurol 2006.
 - Good therapeutic response to valproic acid, phenobarbital and clonazepam. Detrimental effects from vigabatrin, carbamazepine and oxcarbazepine.
- Dion, M. et al, Epilepsia 2007.
 - Lamotrigine is efficacious as adjunctive therapy

Nolt, et al, 2003: Monotherapy

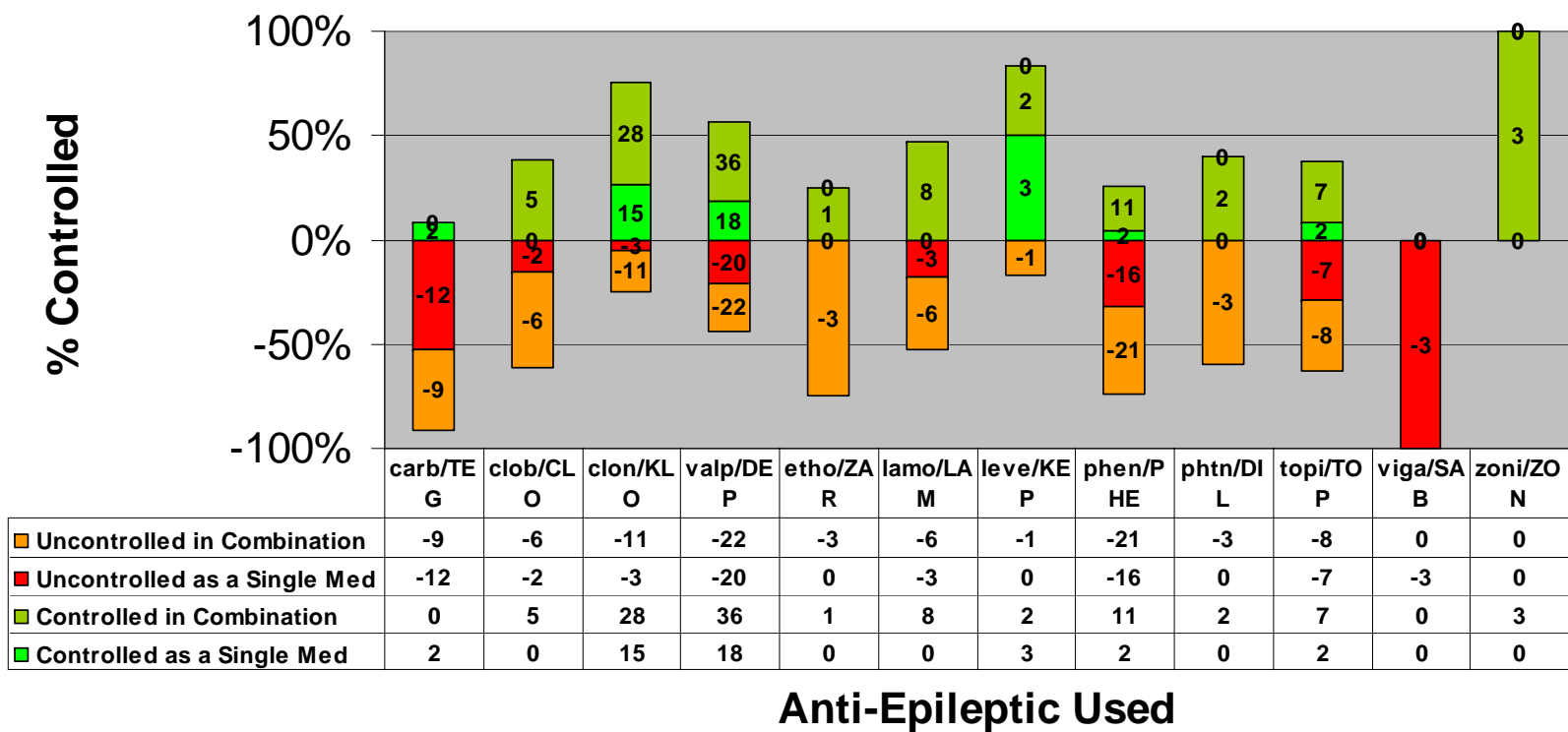
Drug	Sz Frequency	Sz Severity	Behavior
VPA	2.1 (45)	2.2 (42)	2.9 (44)
CBZ	4 (27)	3.7 (27)	4 (27)
TPM	3.1 (20)	2.8 (20)	2.9 (19)
PB	2.8 (18)	2.6 (18)	3.7 (18)
LTG	2.6 (18)	2.4 (18)	2.2 (18)
CLZ	1.9 (13)	2.2 (13)	3.9 (14)
ESM	2.6 (7)	2.4 (7)	3 (7)
CLB	1 (5)	1 (5)	2 (5)
ZSM	1.7 (3)	1.7 (3)	2.7 (3)

Nolt, et al, 2003: Polytherapy

Drugs	Sz Frequency	Sz Severity	Behavior
VPA,CLZ	2.8 (6)	2.7 (6)	4.4 (6)
VPA, TPM	3.8 (4)	3.8 (4)	3 (4)
VPA, TPM, CLZ	3.3 (4)	2.8 (4)	3.3 (4)
VPA,LTG	2.8 (4)	3 (4)	1.6 (4)
PHT,CBZ	3.5 (4)	3.8 (4)	3.3 (4)

Meta-Analysis of Efficacy of Anti-Epileptics in Angelman Syndrome (used in 3 or more patients)

Includes Studies by: Bichell, Schlanger, Dion, Valente, Galvan-Manso
(with Galvan derived from percentages)



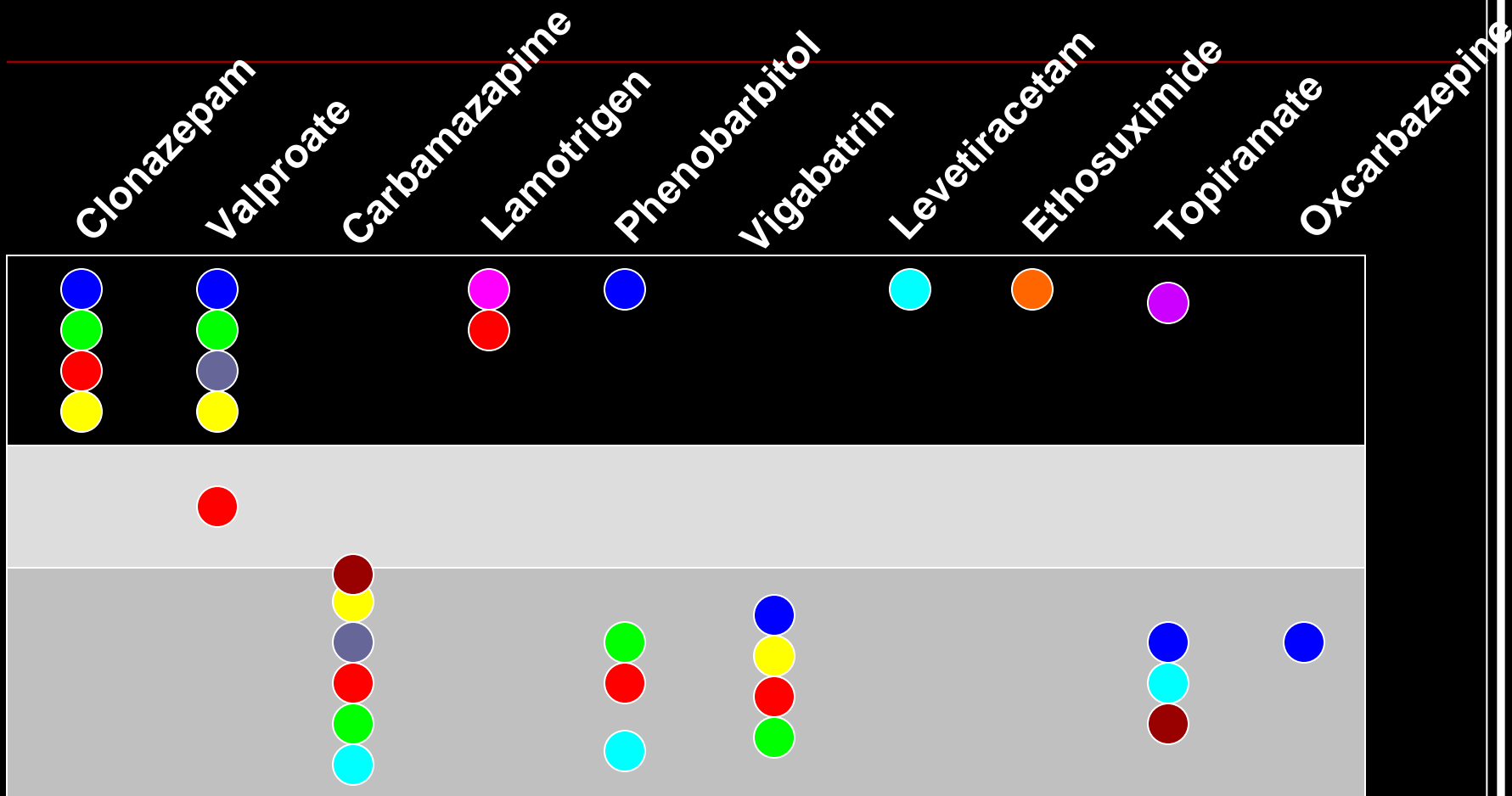
Parent Questionnaire Study: Effectiveness of AED's N=78

Drug	#pts	#Sz	SzSeverity	Alertness	Behavior
VPA	45	+22	+15	-2	-4
CBZ	22	-14	-13	-13	-9
PB	5	0	0	-1	-2
PHT	5	+1	-2	0	-1
ESM	6	-1	0	-2	-3
LTG	13	+12	+7	+4	+5
VGB	9	-3	-3	-8	-3
CLB	5	+2	+2	+4	+1
CLZ	23	+17	+19	+6	+3
NTZ	4	+4	+4	+3	+2

Case Reports

- **Topiramate:** 5 patients, 2 sz free, 2 90% reduction, 1 insomnia/akathisia, Franz, D., Neurology 2000
- **Ethosuximide:** 2 patients treated with high doses attained complete remission along with EEG improvement, Sugiura, C. et al, Neurology 2001
- **Levodopa:** 2 patients, both improved in motor function and seizures, reduced anti-epileptics. Harbord, M., J. Clin Neurosci 2001.
- **Ketogenic diet:** 4 refractory patients, all improved, Valente, M. et al, Arch Neurol 2006.
- **Omega-3 Fatty Acids:** 1 refractory AS patient on topamax and valproate improved greatly with incorporation of omega-3 polyunsaturated fatty acids, Schlanger, S., Epilepsia 2002

Anti-Epileptics in Angelman Syndrome: Summary of the Recommendations



Clobazam 2, Zonisamide 1

Recommendations

- Remember Clonazepam: It works for AS!
- Avoid: carbamazepine, phenobarbital, topiramate, trileptal, vigabatrin
- Potential, need more data: levetiracetam, zonisamide, ethosuximide, ketogenic diet

**Captain
Obvious**



to the rescue!

Types of Seizures

- Did not have standardized descriptions at different sites
- Many absence, febrile, partial tonic-clonic, atonic, myoclonic
- Need long-term follow-up for efficacy and side-effects (all studies are too short-term)

Conclusions

- GABAR3 deletion may be crucial factor in clonazepam efficacy
- Different meds for deletion vs. non-deletion AS patients
- Need more data on deletion class vs. med
- Treat syndrome, not just seizure type
- Promising but unstudied: levetiracetam, zonisamide, ethosuximide, ketogenic diet, levodopa, omega-3 fatty acids, vaso-vagal stimulator
- Look for Thiele, E. et al results of ASF parent survey, reporting at this conference

Acknowledgements

- David Bichell, MD, San Diego and Nashville
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- Erica Sanborn, Boston
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- Art Beaudet, MD, Houston
- Lina Shinawi, Houston

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SAVE THE DATE

SATURDAY, SEPTEMBER 29, 2007 ★ 7:00 P.M.

6TH ANNUAL

ART & WINE PARTY

FOR ANGELMAN SYNDROME RESEARCH

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