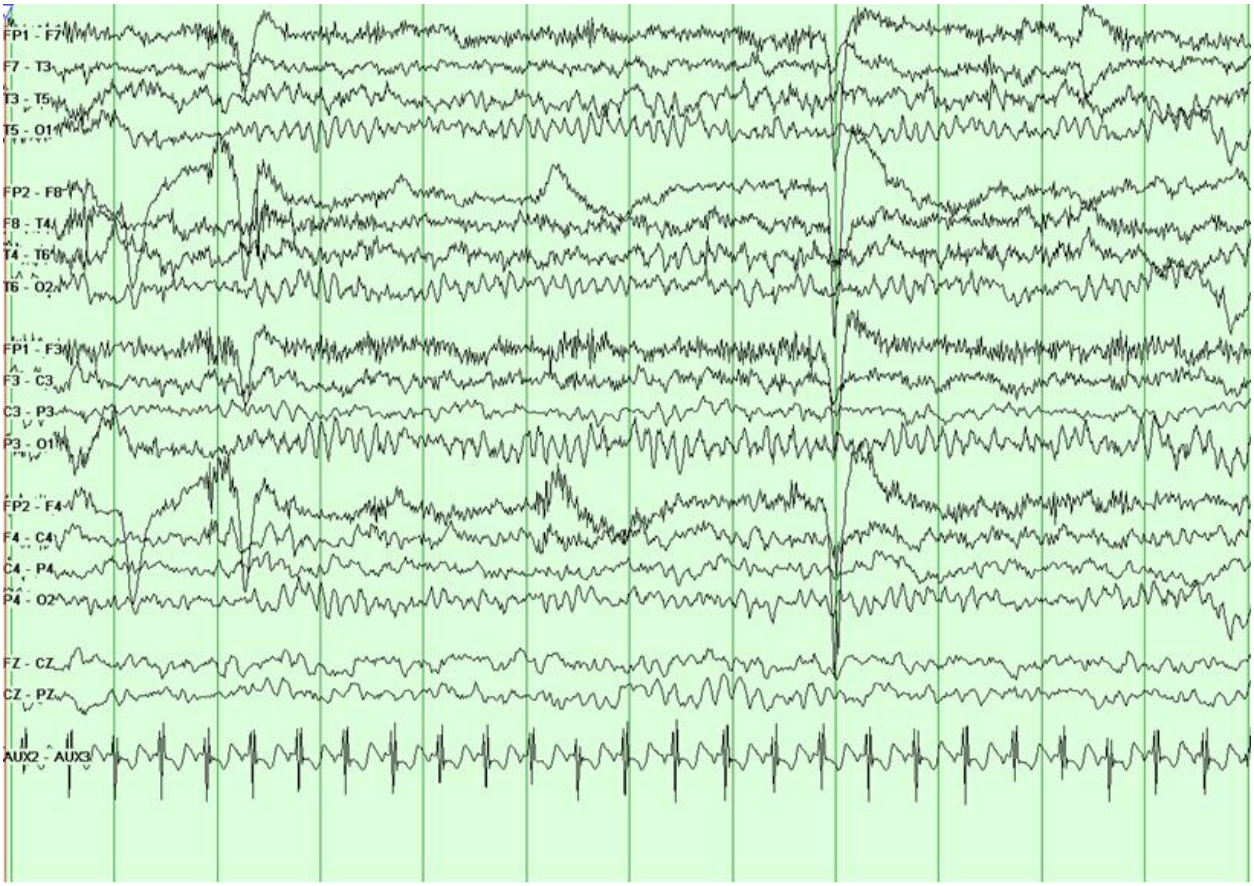
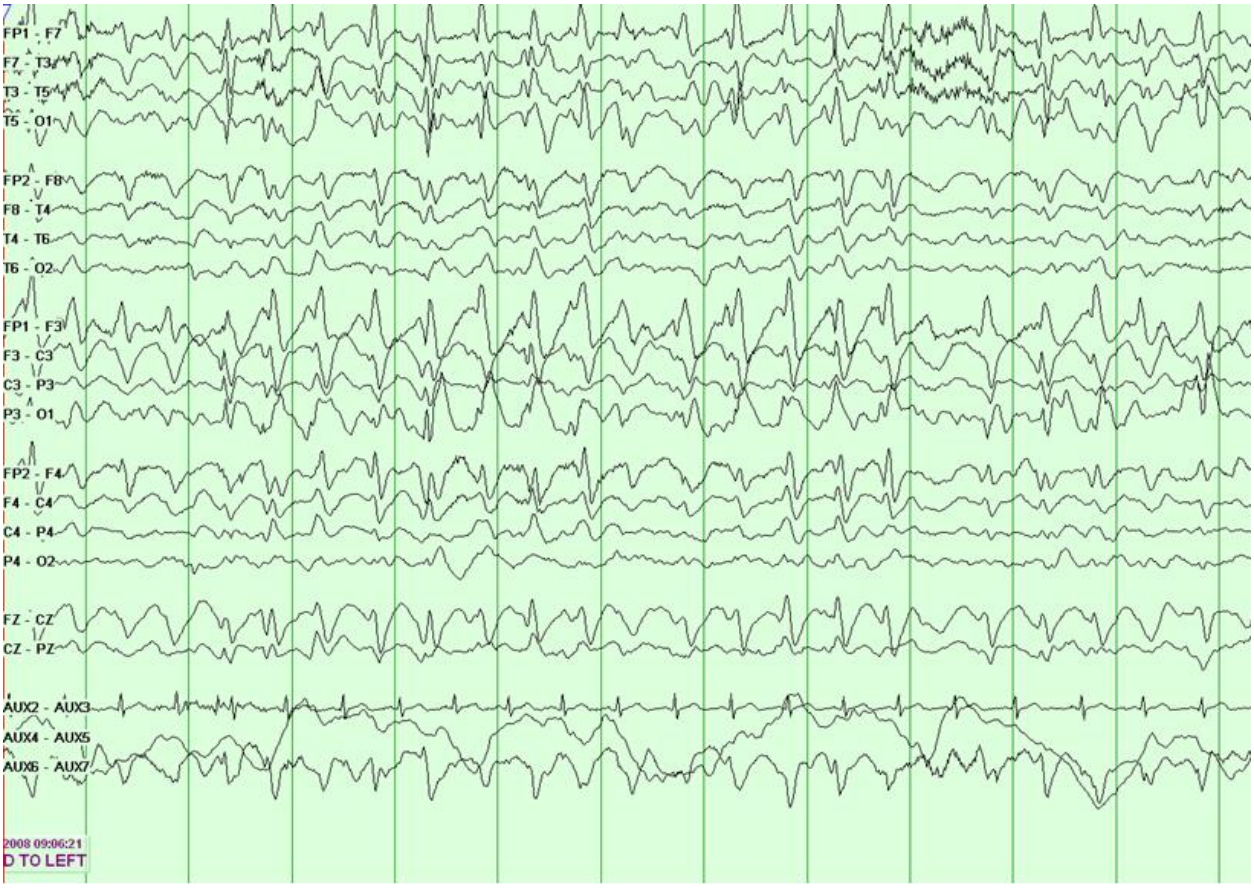
Seizures and Angelman Syndrome

Angelman syndrome (AS) is a neurodevelopmental genetic disorder characterized by global developmental delays, severe speech impairment, disorders of balance or movement (usually ataxia), and frequents laughter, resulting from a defect in the maternally inherited copy of chromosome 15q11-13. AS can result from a deletion of this portion of the chromosome, inheritance of two paternal copies (uniparental disomy), a UBE3A mutation or a defect in the imprinting center. Some individuals meet clinical criteria for AS but do not have a clear genetic diagnosis. Epilepsy is present in over 80% of affected individuals, often presenting with multiple seizure types and is typically refractory to multiple medications.

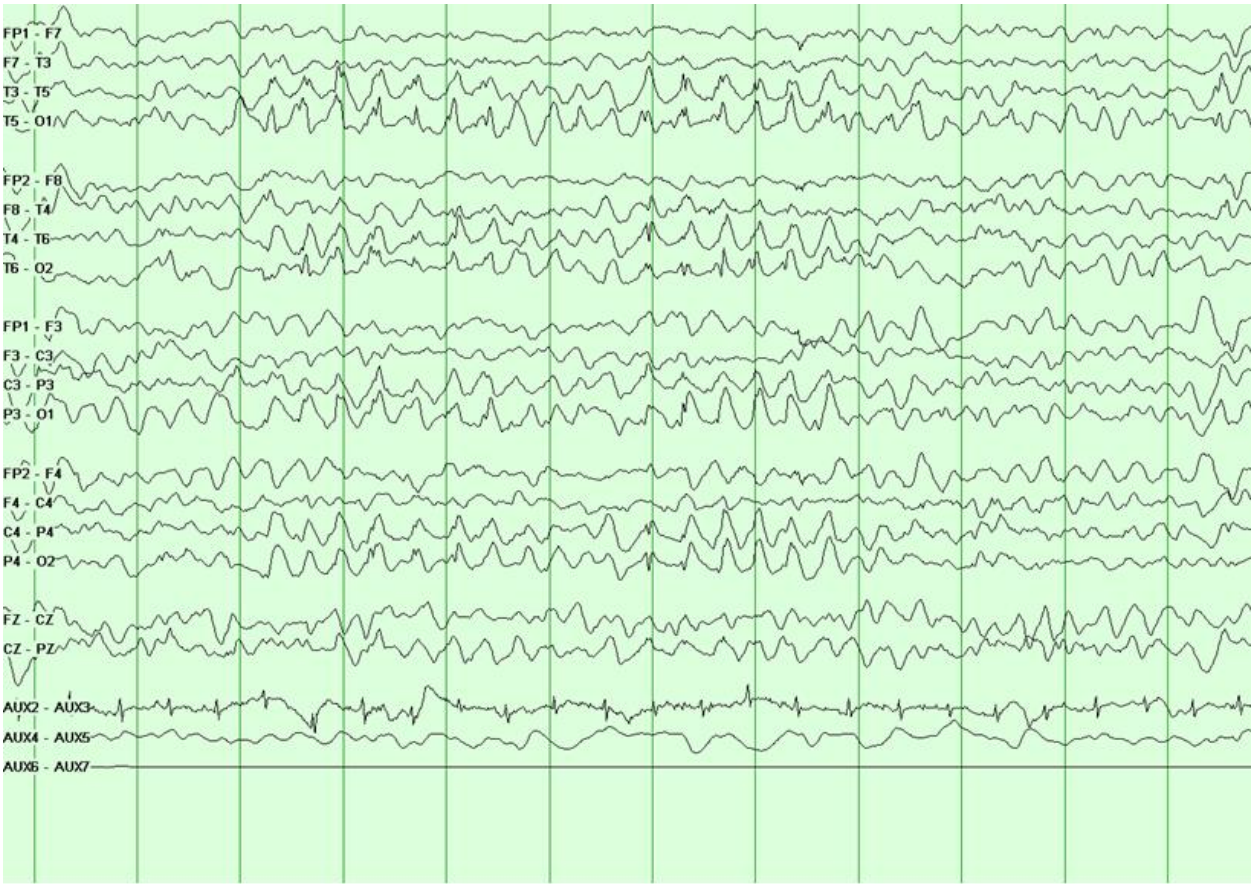
Normal EEG



AS EEG showing typical bi-frontally predominant generalized 2-3Hz spike and slow wave discharges



AS EEG showing typical posterior notched delta activity



Approximately 1,000 families of individuals with AS were contacted through the Angelman Syndrome Foundation (ASF) and asked to complete a questionnaire survey online. The survey contained detailed questions relating to the presence and presentation of epilepsy in AS, genetic subtypes of AS, and progression of epilepsy across the lifespan. Included were free text questions that asked respondents to describe their family member's seizures in detail. The questionnaire additionally included detailed questions regarding the effects of various epilepsy treatments, both pharmacologic and non-pharmacologic, including free text questions asking family members to detail medication side effects.

There were responses from family members of 461 individuals with AS (subjects included in the study). The subjects had an average age of 5.3 years (<1-35 years) at diagnosis, with 65% of subjects having a maternal deletion, 18% with an unknown subtype, 7% each with uniparental disomy (UPD) and UBE3A mutations, and 2% with an imprinting defect (ID).

Of the 461 subjects, 86% had experienced seizures with an average age of seizure onset of 2.9 years. Multiple seizure types are reported in 60% of subjects (average of 1.9 types), and the most frequently reported were atonic seizures (41%), generalized tonic-clonic seizures (40%), and atypical absence seizures (37%). Approximately 32% were reported to have complex partial seizures and 6% simple focal motor seizures. Of those reported to have seizures with partial

onsets, 8% had secondary generalization. Overall, 11% were reported to have only partial onset seizures, while 30% had both partial and generalized seizures. In addition, myoclonic seizures, tonic seizures, infantile spasms, and Lennox-Gastaut Syndrome were also reported (Table 1). Seizure types were determined by detailed free-text descriptions of the seizures provided by family members.

Table 1. *Prevalence and frequency of various seizure types and syndromes in those with epilepsy due to Angelman Syndrome.*

SEIZURE TYPE/SYNDROME	PREVALENCE IN AS	FREQUENCY (SEIZURES/WEEK)
Atonic	41%	21.5
Generalized Tonic-Clonic	40%	9.2
Absence	37%	13.9
Complex Partial	32%	7.9
Myoclonic	12%	18.1
Tonic	9%	10.4
Secondarily Generalized	8%	8.6
Partial/Focal Motor	6%	11.4
Infantile Spasms	2%	12.3
Lennox-Gastaut Syndrome	1%	---

At the time of the survey, 34% were reported to be seizure free for a median period of 3.2 years with 23% experiencing seizure freedom for over 1 year. The average age of seizure freedom was 8.8 years. Of the 396 subjects with seizures, 280 provided adequate data to determine rates of current epilepsy (those with seizure activity over the past year were considered to have “current” epilepsy). These rates are listed in Table 2. In addition, approximately 28% of those over 15 years of age reported an increase in seizure frequency after puberty.

Table 2. *Percentages of those in various age groups with current epilepsy (as defined by seizures in the past year) for the 280/396 with epilepsy who provided adequate data as well as the 65 who never had seizures (N=345).*

AGE (YEARS)	PERCENT WITH CURRENT SEIZURES	TOTAL IN EACH GROUP (N)
<3	46%	30
3-5	60%	58
6-8	61%	51
9-11	71%	42
12-14	52%	46
15-17	53%	45
18 or older	59%	73

While it is unclear what percentage of subjects experience non-convulsive state epilepticus (NCSE), 137 of the 396 with epilepsy (35%) were described as having some regression in development. Of those instances of regression, 96 were attributed to seizure activity while 15 were attributed to medication and the remaining 26 to medical illness, environmental changes, or an uncertain etiology.

There were no statistically significant differences in seizure types or epilepsy rates based on gender, but there were clear differences in rates of epilepsy among genetic subtypes. Those with maternal deletions and unknown subtypes had the highest rates of epilepsy (89% and 90% respectively) while those with ID were the least affected (55%) (Table 3). There were no significant differences in seizure types amongst the different genetic subtypes, except for the more catastrophic epilepsies such as infantile spasms and Lennox-Gastaut Syndrome only occurring in those with deletions or unknown subtypes (Table 3).

Table 3. *Prevalence of various genetic subtypes I Angelman syndrome with associated rates of epilepsy, multiple seizure types, and catastrophic epilepsy syndromes.*

GENETIC MUTATION	% OF THOSE WITH AS	% OF THOSE WITH EPILEPSY	% WITH MULTIPLE TYPES	% WITH IS OR LGS
Maternal Deletion	65%	89%	72%	4%
Unknown/Clinical	18%	90%	60%	3%
Uniparental Disomy	7%	75%	38%	0%
UBE3A Mutation	7%	74%	80%	0%
Imprinting Defect	2%	55%	80%	0%

1. IS – infantile spasms

2. LGS – Lennox Gastaut Syndrome

The most commonly prescribed medications amongst subjects with epilepsy were valproic acid (VPA – 62%), clonazepam (CZP – 34%), phenobarbital (PB – 30%), topiramate (TPM – 30%), carbamazepine (CBZ – 24%), lamotrigine (LTG – 24%), and levetiracetam (LEV – 20%). The complete list of medications is located in Table 4 along with average doses and lengths of treatment for the most commonly used medications. At the time of the study, subjects were on an average of 1.2 current medications, with 40% currently on monotherapy and 64% having tried multiple medications (average of 3.2 medications). Only 15% achieved good seizure control with their initial AED and an additional 8% with a second agent, with the remaining 77% refractory to medication.

Table 4. *Percentage of individuals with AS and epilepsy who have tried various anti-epileptic drugs (AEDs), with average dose (mg/kg/day) and length of treatment for whom that information was available.*

MEDICATION	PERCENTAGE TRIED	AVG DOSE (MG/KG/DAY)	AVG COURSE OF TREATMENT
Valproic Acid	62%	16 (N=86)	51 months
Clonazepam	34%	0.4 (N=40)	36 months
Phenobarbital	30%	31. (N=9)	14 months
Topiramate	30%	4.4 (N=28)	30 months
Carbamazepine	24%	7.3 (N=3)	33 months
Lamotrigine	24%	8.1 (N=24)	13 months
Levetiracetam	20%	44.4 (N=23)	20 months
Phenytoin	20%	----	----
Zonisamide	10%	----	----
Ethosuxamide	8%	----	----
Gabapentin	7%	----	----
Felbamate	7%	----	----
Oxcarbazepine	5%	----	----
Tranxene	4%	----	----
Clobazam	4%	----	----
ACTH	2%	----	----
Nitrazapam	2%	----	----
Other	5%	----	----

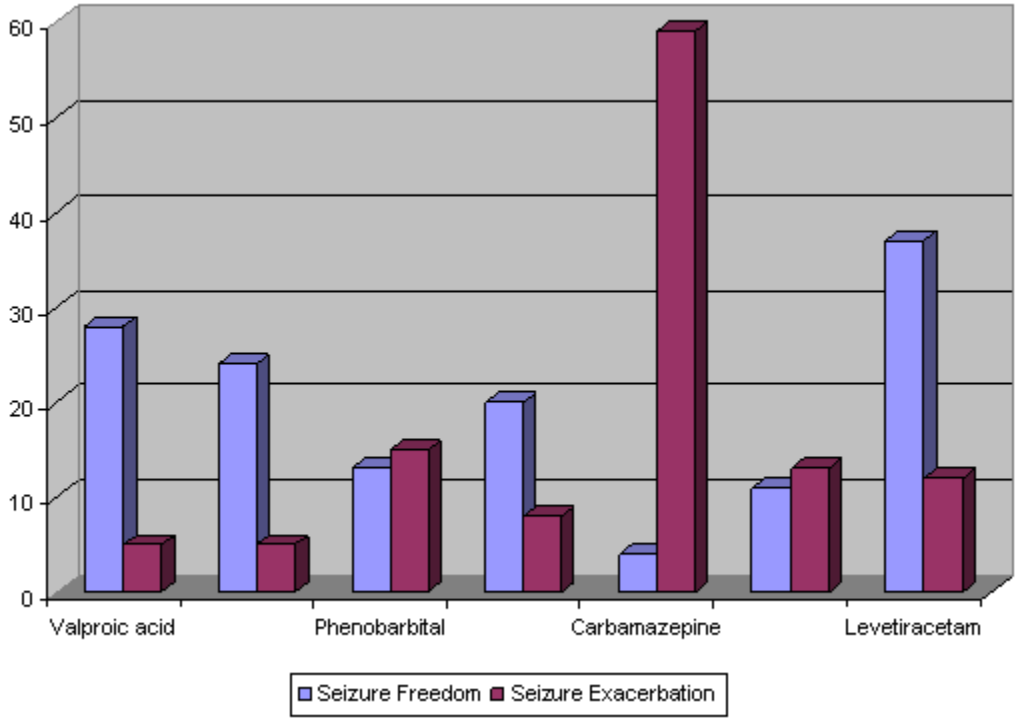
1. “Other” includes pregabalin, mysoline, and vigabatrin.

Subjects’ family members were asked which medications worked best in controlling their epilepsy if they had tried multiple medications. VPA (25%) had the highest response rate followed by LEV (18%), LTG (17%), and TPM (14%). The lowest response rates were to CBZ (2%) and PB (2%). Similarly, LEV (37%) and VPA (28%) were associated with the highest rates of seizure freedom, followed by CZP (24%) and TPM (20%), with CBZ (4%) having the lowest rate. CBZ, by far, was associated with the highest rate of seizure exacerbation (59%), followed by PB (15%). See Table 5 for a complete list.

Table 5. *Efficacy of the 7 most commonly prescribed medications as evidenced by the percent that felt the medication worked best for them (of those who tried multiple medications), as well as those who felt the medication provided a period of seizure freedom or exacerbation.*

MEDICATION	WORKED BEST	SEIZURE FREEDOM	SEIZURE EXACERBATION
Valproic acid	25%	28%	5%
Clonazepam	11%	24%	5%
Phenobarbital	2%	13%	15%
Topiramate	14%	20%	8%
Carbamazepine	2%	4%	59%
Lamotrigine	17%	11%	13%
Levetiracetam	18%	37%	12%

Rates of seizure freedom and seizure exacerbation for the most commonly prescribed AED in AS

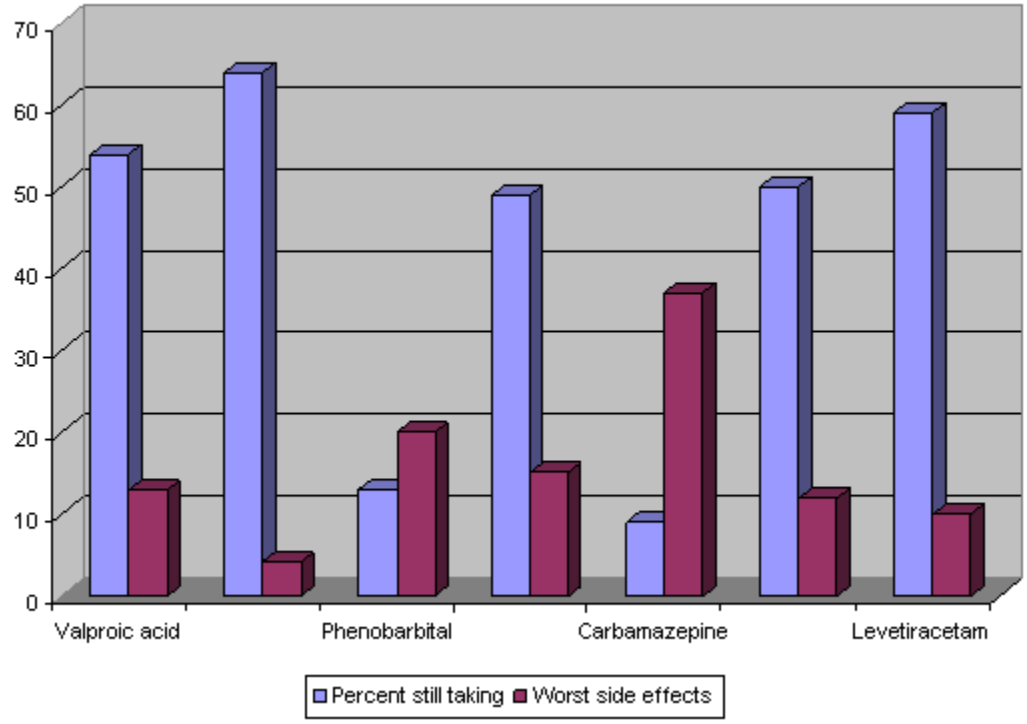


Of the seven most commonly prescribed medications, approximately 50% or more of subjects who had tried CZP (64%), LEV (59%), VPA (54%), LTG (50%), and TPM (49%) were still on that medication at the time of the survey, whereas only 13% of those who had tried PB and 9% of those who had tried CBZ were still on those medications at the time of the survey, indicating these medications may have better tolerability and efficacy than PB and CBA. Similarly, CBZ (45%) and PB (32%) were most frequently associated with intolerable side effects, followed by TPM (22%), VPA (17%), LTG (17%), LEV (14%) and CZP (5%). VPA did, however, have some potentially serious side effects with 3 patients reporting pancreatitis, 4 patients temporarily losing the ability to ambulate, 5 experience a drop in platelets, and one other experiencing a decreased white blood cell count. There was also one child on LTG who developed Stevens-Johnson syndrome. See Table 6 for a complete list as well as the most common side effects for each medication.

Table 6. *Tolerability of the 7 most commonly prescribed medications as evidenced by the percent still taking each medication and the percent that reported intolerable side effects, with the most common side effects listed for each medication.*

MEDICATION	% STILL TAKING	WORST SIDE EFFECTS	OTHER SIDE EFFECTS	MOST COMMON SIDE EFFECTS
Valproic acid	54%	13%	4%	Tremor (8%)
				Fatigue (7%)
Clonazepam	64%	4%	<1%	Fatigue (8%)
				Hypotonia (6%)
Phenobarbital	13%	20%	12%	Lethargy (14%)
				Irritability (9%)
Topiramate	49%	15%	7%	Weight loss (8%)
				Cognitive slowing (7%)
Carbamazepine	9%	37%	8%	Increased seizures* (20%)
				Fatigue (6%)
Lamotrigine	50%	12%	5%	Rash (%)
				Fatigue (5%)
Levetiracetam	59%	10%	4%	Lethargy (5%)
				Irritability (4%)

Percentages of those still taking each of the most commonly prescribed AED in AS as well as percentages of those who felt each AED had the most intolerable side effects.



Approximately 17% of subjects tried non-pharmacologic therapies for their epilepsies. The most common was dietary therapy with 40 subjects (11%) having tried this modality including 31 (8%) on the classic ketogenic diet, 7 (2%) on the low glycemic index treatment (LGIT), and 2 (~1%) on non-standardized diets. In addition to dietary therapies, 16 (4%) subjects had a vagus nerve stimulator (VNS) implanted (Table 7).

Table 7. *Efficacy and tolerability of non-pharmacologic treatments for epilepsy in AS as evidenced by the percent of those for whom the treatment worked best and the percent still using each treatment.*

TREATMENTS	% TRIED	WORKED BEST	STILL USING
Ketogenic Diet	8%	36%	19%
Low Glycemic Index Therapy	2%	0%	57%
Vagal Nerve Stimulator	4%	17%	50%

This is the largest study to date examining epilepsy and its treatments in AS. Epilepsy is very common in AS and, typically, quite refractory to medication. Although epilepsy in AS is considered a generalized epilepsy, apparent partial onset seizures were fairly prevalent, though they did not respond well to medications, such as CBA, which are used to treat focal seizures and typically exacerbate generalized epilepsies. Epilepsy was most severe in those with maternal deletions but,

interestingly, the 18% of subjects who had an unknown/clinical diagnoses had epilepsy rates similar to those with deletions (90%), and the more catastrophic epilepsies such as infantile spasms and Lennox-Gastaut syndrome were only seen in those with deletions or unknown subtypes. Another significant finding of this study is that newer AED's, specifically LEV and LTG, and to a lesser extent TPM, appear to have similar efficacies in treating epilepsy in AS as compared to the older, more commonly prescribed medications (VPA, CZP) and have similar or possibly better side effect profiles with no need for routine blood monitoring (as with VPA), and less risk of potentially serious side effects. Non-pharmacologic therapies such as dietary therapy and VNS also show favorable efficacy and tolerability, but due to small sample size further studies are needed. Further characterization of epilepsy in AS, in addition to advances in genetic analyses, will hopefully lead to a better understanding of the pathogenesis of epilepsy in this populations and, ultimately, better approaches to effectively treat epilepsy in AS.

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