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FULL-LENGTH ORIGINAL RESEARCH

Epilepsy in Angelman syndrome: A questionnaire-based assessment of the natural history and current treatment options

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SUMMARY

Purpose: Angelman syndrome (AS) commonly presents with epilepsy (>80%). The goal of this study was to examine the natural history and various treatments of epilepsy in AS in a large population.

Methods: A detailed electronic survey containing comprehensive questions regarding epilepsy in AS was conducted through the Angelman Syndrome Foundation.

Results: There were responses from 461 family members of individuals with AS, of whom 86% had epilepsy (60% with multiple seizure types), the most common being atonic, generalized tonic–clonic, absence, and complex partial. Partial-onset seizures only were reported in 11% of those with epilepsy. Epilepsy was most common among those with maternal deletions and unknown subtypes, with catastrophic epilepsies present in only these two subtypes. These epilepsies were refractory to medication, with only 15% responding to the first antiepileptic drug (AED). The most commonly prescribed AED were valproic acid and clonazepam, but lamotrigine and levetiracetam appeared to have similar efficacy and tolerability.

Discussion: This is the largest study to date assessing epilepsy in AS. Although epilepsy in AS is considered a generalized epilepsy, there was a high prevalence of partial seizures. There are few previous data regarding the use of newer AED in AS, and the results of this study suggest that these newer agents, specifically levetiracetam and lamotrigine, may have efficacy similar to that of valproic acid and clonazepam, and that they appear to have similar or better side-effect profiles. Nonpharmacologic therapies such as dietary therapy and vagus nerve stimulation (VNS) also suggest favorable efficacy and tolerability, although further studies are needed.

KEY WORDS: Epilepsy, Angelman syndrome, Chromosome 15, Antiepileptic medications.

Angelman syndrome (AS) is a neurodevelopmental genetic disorder consisting of multiple genetic subtypes, first described in 1965 (Angelman, 1965), and characterized by global developmental delays, severe speech impairment, disorders of balance or movement (usually ataxia), and frequent laughter, with epilepsy present in more than 80% of affected individuals (Williams et al., 2006). The incidence of AS is estimated to be between 1 in 10,000 and 1 in 20,000 (Williams, 2005), and up to 7% of children with severe epilepsy and mental retardation with severe speech impairment may have AS (Buoni et al., 1999).

The most common genetic subtype causing AS is a maternal deletion of chromosome 15q11–13 (68–75%), followed by unknown/clinical (10–20%), *UBE3A* mutations (8–11%), uniparental disomy (UPD 2–7%), and imprinting defects (ID 2–5%) (Williams et al., 2001). Previous studies consistently demonstrate that those with

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maternal deletions have the highest rates of epilepsy as well as the most severe epilepsy phenotypes as compared to other subtypes (Minassian et al., 1998; Laan et al., 1999a, 1999b; Lossie et al., 2001; Brockmann et al., 2002; Valente et al., 2003; Varela et al., 2004; Valente et al., 2005).

Epilepsy in AS typically presents with multiple seizure types (Ruggieri & McShane, 1998; Ostergaard & Balslev, 2001; Nolt et al., 2003). It is typically considered a generalized epilepsy, with atypical absence, atonic, generalized tonic–clonic, and myoclonic the most frequent seizure types, but complex partial seizures have also been reported in 13–39% of those with epilepsy (Casara et al., 1995; Buoni et al., 1999; Nolt et al., 2003; Ohtsuka et al., 2005; Valente et al., 2005, 2006), including seizures with occipital lobe semiology consisting of eye deviation and vomiting (Viani et al., 1995). Sporadic cases of infantile spasms have been reported as well (Galvan-Manso et al., 2005a, 2005b; Uemura et al., 2005; Paprocka et al., 2007). Nonconvulsive status epilepticus (NCSE) is common (Pelc et al., 2008), but reports on the prevalence of both convulsive status epilepticus and NCSE are variable, with reported rates of NCSE as high as 91% (Ohtsuka et al., 2005). Children with Angelman syndrome can also develop myoclonic status with nonprogressive encephalopathies. This is a rare epilepsy syndrome, but 37% of subjects in a recent study assessing this had AS (Dalla Bernardina et al., 2005).

Epilepsy in AS typically begins in early childhood (Galvan-Manso et al., 2005a,b) and appears to improve around puberty, but seizures often return during adulthood (Buckley et al., 1998; Clayton-Smith, 2001; Pelc et al., 2008), with some studies reporting epilepsy rates greater than 80% in adulthood (Buntinx et al., 1995; Laan et al., 1997, 1999a, 1999b).

Epilepsy in AS is often refractory to multiple medications, with two of the previously mentioned case series reporting combination therapy in 47% (Nolt et al., 2003) and 60% (Laan et al., 1999a, 1999b) of subjects respectively. The literature has demonstrated that valproic acid (VPA) is the most commonly prescribed antiepileptic drug (AED) in AS (Laan et al., 1999a, 1999b; Nolt et al., 2003; Valente et al., 2006), with other commonly prescribed AED including clonazepam (CZP), carbamazepine (CBZ), phenobarbital (PB), topiramate (TPM), and lamotrigine (LTG). Several prior studies have reported that VPA and CZP, either alone or in combination with each other or other medications, were the most effective medications in controlling seizures (Laan et al., 1999a, 1999b; Nolt et al., 2003; Galvan-Manso et al., 2005a, 2005b; Valente et al., 2006), whereas in another study (Ostergaard & Balslev, 2001) it was argued that benzodiazepines, specifically nitrazepam (NZP), clobazam (CLB), and CZP, were most effective. Several other studies reported that CBZ, vigabatrin (VGB), and oxcarbazepine (OXC) exacerbated seizures in AS (Laan et al., 1997; Kuenzle et al., 1998; Ostergaard & Balslev, 2001; Nolt et al., 2003; Valente et al., 2006). There are few studies examining the efficacy and tolerability of specific AED, with recent smaller studies having reported good efficacy and tolerability with ethosuximide (ESM) (Sugiura et al., 2001), TPM (Franz et al., 2000), and LTG (Dion et al., 2007).

Few data have been published on dietary therapy, with one study (Valente et al., 2006) reporting four children placed on the classic ketogenic diet to treat refractory epilepsy with all four being treated effectively, and another (Laan et al., 1999a, 1999b) reporting improved seizure control in one child on the ketogenic diet. There are no previous data on the low glycemic index treatment (LGIT), vagus nerve stimulation (VNS), or surgical intervention in the treatment of refractory epilepsy in AS.

This study will examine the course of epilepsy in AS, including typical seizure types, frequencies, associations with various genetic subtypes, and the progression of epilepsy over the lifespan. It will also examine the efficacy and tolerability of various AED, including the less frequently studied newer AED, as well as nonpharmacologic therapies such as dietary therapy and VNS in treating epilepsy in a large cohort of individuals with AS.

Methods

Approximately 1,000 families of individuals with AS were contacted through the Angelman Syndrome Foundation (ASF) and asked to complete a questionnaire survey online (Questionnaire S1). The first 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, including free-text questions asking family members to detail medication side effects. The study was additionally advertised as a research project on the ASF website to further recruit from an unknown number of potential respondents. The survey was available online for 3 months, from February–May 2007. This study was approved by our institution's (Massachusetts General Hospital) institutional review board (IRB) prior to the recruitment of subjects.

Results

There were responses from family members of 461 individuals with AS (subjects included in the study), representing a response rate of roughly 40–50%. The subjects had an average age of 13.9 years (1.3–45 years) at the time of the survey, with an average age of 5.3 years (<1–35 years) at diagnosis. Approximately 56% of the subjects were male.

Of the 461 subjects, 86% had experienced seizures with an average age of seizure onset of 2.9 years. Multiple seizure types were 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 (either focal motor, complex partial, or both), whereas 30% had both partial and generalized seizures. In addition, myoclonic and tonic seizures, as well as epilepsy syndromes such as infantile spasms, and Lennox-Gastaut syndrome were also reported. The majority of subjects reported seizure frequencies, and average frequencies were calculated as seizures per week (Table 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 more than 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 who were seizure free for more than a year considered not to have current seizures). Only 46% of those age <3 years had current seizures, whereas 64% of those ages 3–11 years, 53% of those ages 12–17 years, and 59% of those age 18 and older had current seizures (Table 2). Approximately 28% of those older than 15 years of age reported an increase in seizure frequency after puberty.

Of the 396 individuals with epilepsy, 48 (12%) were reported to have experienced convulsive status epilepticus (as defined as seizures lasting over 15 min or clusters of seizures lasting that long with no return to baseline between events). This, however, was the one question in the survey with a low response rate, with only 75 responses to this question. Therefore, 48 of the 75 respondents (64%) who answered the question had family members who experienced convulsive status epilepticus. Of the 48 who experienced convulsive status epilepticus, 28 individuals (58%) were reported to have had five or fewer episodes total; 3 only experienced episodes that were provoked. Of the remaining 20, 12 had very frequent episodes of convulsive status epilepticus, and the other 8 did not have reported frequencies. Approximately 64% of subjects with epilepsy used an emergency medication for prolonged seizures or clusters of seizures. The two most commonly used medications were lorazepam (LZP, 29%) and diazepam (DZP, 28%), with 1% or less using midazolam, CZP, PB, phenytoin, chloral hydrate, NZP, prednisolone, and fosphenytoin (PHT).

Table 1. Prevalence and frequency of various seizure types and epilepsy syndromes in those with epilepsy due to Angelman syndrome (AS)

Seizure type	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
Epilepsy syndromes		
Infantile spasms	2	–
Lennox-Gastaut syndrome	1	–

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

Age (years)	Percentage 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

Although it is unclear what percentage of subjects experienced NCSE, 137 of the 396 with epilepsy (35%) were described as having some regressions in development. Of those instances of regression, 96 were attributed to seizure activity, whereas 15 were attributed to medications, and the remaining 26 to medical illness, environmental changes, or an uncertain etiology.

There were no statistically significant differences in seizure types based on gender, but there were clear differences in rates of epilepsy among genetic subtypes. Of all the subjects in the study, 65% had a maternal deletion, 18% had an unknown subtype, 7% each had UPD and *UBE3A* mutations, and 2% had ID. Those with maternal deletions (89%) and unknown subtypes (90%) had the highest rates of epilepsy, whereas those with ID (55%) were the least affected (Table 3). There were no significant differences in seizure types among 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).

The most commonly prescribed medications among subjects with epilepsy were VPA (62%), CZP (34%), PB (30%), TPM (30%), CBZ (24%), LTG (24%), and LEV

Table 3. Prevalence of various genetic subtypes in Angelman syndrome (AS) with associated rates of epilepsy, multiple seizure types, and catastrophic epilepsy syndromes

Genetic mutation	Percentage of those with AS	Percentage with epilepsy	Percentage with multiple seizure types	Percentage 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

IS, infantile spasms; LGS, Lennox-Gastaut syndrome.

(20%). The complete list of medications used 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 had 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% responded to their initial AED, and an additional 8% responded to the second agent, with the remaining 77% refractory (epilepsy not currently well controlled).

Table 4. Percentage of individuals with Angelman syndrome (AS) and epilepsy who have tried various antiepileptic drugs (AED), with average dose (mg/kg/day) and length of treatment for whom that information was available

Medication	Percentage tried	Average dose (mg/kg/day) (n)	Average course of treatment (months)
Valproic acid	62	16 (86)	51
Clonazepam	34	0.4 (40)	36
Phenobarbital	30	3.1 (9)	14
Topiramate	30	4.4 (28)	30
Carbamazepine	24	7.3 (3)	33
Lamotrigine	24	8.1 (24)	13
Levetiracetam	20	44.4 (23)	20
Phenytoin	20	–	–
Zonisamide	10	–	–
Ethosuximide	8	–	–
Gabapentin	7	–	–
Felbamate	7	–	–
Oxcarbazepine	5	–	–
Clorazepate	4	–	—
Clobazam	4	–	–
ACTH	2	–	–
Nitrazepam	2	–	–
Other	5	–	–

"Other" includes pregabalin, Mysoline, and vigabatrin.
ACTH, adrenocorticotropic hormone.

Subjects' family members were asked which medications worked best in controlling each subject's 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%). The following pertain to all subjects who tried each medication: 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.

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, suggesting that CZP, LEV, VPA, LTG, and TPM may have better tolerability and efficacy than PB and CBZ. 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 three patients reporting pancreatitis, four patients temporarily losing the ability to ambulate, five experiencing 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.

Approximately 17% of subjects tried nonpharmacologic 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,

Table 5. Perceived efficacy of the seven most commonly prescribed medications as evidenced by the percentage of patients who 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

Table 6. Perceived tolerability of the seven most commonly prescribed medications as evidenced by the percentage of patients still taking each medication and the percentage who reported intolerable side effects, with the most common side effects listed for each medication

Medication	Percentage still taking	Worst side effects (%)	Other side effects (%)	Most common side effects	Potentially serious side effects
Valproic acid	54	13	4	Increased tremor (8%); fatigue (7%)	Pancreatitis (n = 3); Loss of ambulation (n = 4); Thrombocytopenia (n = 5); Leukopenia (n = 1)
Clonazepam	64	4	<1	Fatigue (8%); hypotonia (6%)	None reported
Phenobarbital	13	20	12	Lethargy (14%); irritability (9%)	None reported
Topiramate	49	15	7	Weight loss (8%); cognitive slowing (7%)	None reported
Carbamazepine	9	37	8	Increased seizures (20%)[a]; fatigue (6%)	None reported
Lamotrigine	50	12	5	Rash (6%); fatigue (5%)	Stevens-Johnson syndrome (n = 1)
Levetiracetam	59	10	4	Lethargy (5%); irritability (4%)	None reported

[a]Twenty percent perceived the seizure exacerbation to be "intolerable" as compared to the 59% overall who reported seizure exacerbation with CBZ (Table 2).

Table 7. Perceived efficacy and tolerability of alternate treatments for epilepsy in Angelman syndrome as evidenced by the percentage of those for whom the treatment worked best and the percentage still using each treatment

Treatment	Percentage tried	Worked best	Still using
Ketogenic diet	8 (31)	36 (11)	19 (6)
Low glycemic index therapy	2 (7)	0 (0)	57 (4)
Vagus nerve stimulation	4 (16)	19 (3)	50 (8)

Values are expressed as % (n).

7 (2%) on the LGIT, and 2 (~1%) on nonstandardized diets. Of the 31 subjects on the classic ketogenic diet, six (19%) were still on the diet at the time of the survey, and it was reported to be the best overall treatment for 11 (36%). A higher percentage of subjects were still on the LGIT (57%) at the time of the survey, but it was not reported to be the most effective treatment for any of the subjects. In addition to dietary therapies, 16 subjects (4%) had tried VNS and 11 (3%) were reported to have had other surgical intervention (the nature of these surgeries were unspecified). Of those who had tried the VNS, 50% were still actively using the VNS, and it was reported to be the most effective treatment for epilepsy in 19% (Table 7).

Discussion

This is the largest study to date examining epilepsy and its treatments in AS. The major goal of this study was to assess current treatments for epilepsy in AS, as the current literature regarding newer AED as well as nonpharmacological data in this population is lacking. A retrospective questionnaire-based design was used to achieve as high a response rate as possible, and that goal was achieved. The design, however, has inherent limitations, specifically that the data are based on parental (or family member) responses to questions and not on medical records or raw data [including electroencephalography (EEG) and magnetic resonance imaging (MRI)]. The respondents, in general, are highly motivated, with many maintaining copies of their family member's medical records, but the potential for misreporting still exists, although it is difficult to ascertain the extent.

Epilepsy was found to be very common in this population (86%), which is consistent with the Consensus for Diagnostic Criteria (>80%) (Williams et al., 2006), and similar to previous studies (Ruggieri & McShane, 1998; Valente et al., 2005). The percentage of those with multiple seizure types (60%) is somewhat lower than previous reports from smaller cohorts ranging from 71–90% (Ruggieri & McShane, 1998; Ostergaard & Balslev, 2001; Nolt et al., 2003), which may be due in part to underreporting, especially from family members of older individuals who have been seizure free for some time.

The most common seizure types reported were atonic seizures, generalized tonic–clonic seizures, and atypical absence seizures, which is consistent with previous studies. Although epilepsy in Angelman syndrome is considered generalized epilepsy, partial-onset seizures were fairly prevalent, which has been reported previously (Ruggieri & McShane, 1998; Buoni et al., 1999; Nolt et al., 2003; Ohtsuka et al., 2005; Valente et al., 2006). Over 3% of those in this study reported catastrophic epilepsy syndromes such as infantile spasms and Lennox-Gastaut syndrome. Although there have been sporadic reports of spasms, Lennox-Gastaut syndrome has not been well reported in this population. It is possible this syndrome is underreported not only in this sample, but also in the AS population overall. In addition, these epilepsy syndromes, more so than the seizure types, are prone to misreporting.

Myoclonic seizures, however, were reported in only 12% of individuals in this study, with previous studies demonstrating myoclonic seizures as a predominant seizure type (Guerrini et al., 1996), with prevalence rates between 40% and 50% (Ruggieri & McShane, 1998; Nolt et al., 2003). These seizures may have been underreported in this study, as seizure types were determined by parental descriptions, and seizures were classified as myoclonic only if they could be clearly distinguished from focal motor seizures or generalized tonic–clonic seizures, which again illustrates one of the major difficulties encountered with questionnaire studies. Similarly, the incidence of partial onset seizures may also be inaccurately reported.

Seizures in this population had an early onset and highest prevalence in childhood, followed by a relative decrease around puberty and a slight increase in those ages 18 and older. These age-related prevalence rates are all underestimated, as 116 of 391 with seizures were excluded from the analysis because it was not clear from the data provided if their seizures were current (presence of seizures in the past year). This progression of epilepsy across the lifespan is consistent with prior reports.

The distribution of genetic subtypes in this sample is consistent with previous studies, indicating that this sample is likely representative of the overall AS population, although the percentage of those with unknown subtypes may be higher than expected if families that were unaware of the exact molecular subtype simply listed their family member as ''unknown.'' The percentage of those with seizures in each genetic subtype is also fairly consistent with prior studies, with those with maternal deletions having the highest rates of epilepsy, followed by UPD, *UBE3A*, and ID. Interestingly, the 18% of subjects who had unknown/clinical diagnoses had epilepsy rates similar to those with deletions (90%), and the more catastrophic epilepsy syndromes such as infantile spasms and Lennox-Gastaut syndrome were only seen in those with deletions or unknown subtypes. This similarity between these two groups is of significant interest, and better characterizing those with unknown subtypes using techniques such as comparative genomic hybridization will likely expand our understanding of the pathogenesis of epilepsy in AS (Lawson-Yuen et al., 2006).

The high prevalence (77%) of subjects with epilepsy that was medically refractory appears consistent with nearly all previously published reports. The response rate to initial AED therapy (15% for the first AED and 8% for the second) is significantly lower than the reported response rate for the general adult population to the first AED tried (47%) (Kwan & Brodie, 2001). The most commonly used AED in this study were VPA and CZP, which is consistent with the literature. The majority of larger studies examining treatments of epilepsy in AS were performed in the 1990s and, therefore, there have been few data on the newer AED such as TPM, LTG, and especially levetiracetam (LEV).

The results of this study suggest that both VPA and CZP are not only efficacious, but also well tolerated, as evidenced by the high rates of subjects still taking them and the relatively low rates of intolerable side effects. These medications are perceived to be much better tolerated than CBZ and PB, which show low rates of those still taking them as well as relatively high rates of intolerable side effects. CBZ also had a very high rate of seizure exacerbation. VPA and CZP also appeared to be more efficacious than CBZ and PB, with higher percentages of patients who felt they were the most effective medication in controlling seizures and higher rates of seizure freedom. These findings are all fairly consistent with previously published data.

The three newer AED that were most commonly prescribed (TPM, LTG, and LEV) also all had better perceived efficacy and tolerability than CBZ and PB. Rates of intolerable side effects of LTG and LEV were similar to that of VPA, as were rates of subjects still taking each medication. TPM had a higher rate of intolerable side effects and slightly lower rate of those still taking it. In terms of efficacy, TPM, LTG, and LEV all were fairly comparable to VPA and CZP as far as the percentage of those who felt that medication worked best for them, and LEV had the highest rate of seizure freedom of all the most commonly prescribed AED. There are few previous data examining these newer medications in this population (Franz et al., 2000; Dion et al., 2007).

Another problem inherent in retrospective studies is that variables are not controlled. In this study, patients' medications were not controlled, and there were no standard protocols. The analyses of which medications were most effective and which had the most intolerable side effects took into account all subjects that had tried more than one medication, regardless of how many medications or which medications were tried. Therefore, comparisons were made between subjects on different medication regimens. Analyses of seizure freedom, seizure exacerbation, and overall intolerable side effects were not affected, as there were no subjective comparisons to other medications.

The results also show that a fair proportion of individuals (17%) have also tried nonpharmacologic therapies for their epilepsies. The classic ketogenic diet appeared to be the most efficacious (36% reported it was the most successful treatment), but it was likely not tolerated as well as the LGIT (57% still on LGIT as opposed to 19% on the ketogenic diet), although the sample is too small to draw any significant conclusions.

Epilepsy is very common in AS and, typically, refractory to medication. 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 population and, ultimately, better approaches to effectively treat epilepsy in AS. Another significant finding of this study is that newer AED, specifically LEV and LTG, and to a lesser extent TPM, are perceived to have similar efficacies in treating epilepsy in AS, as compared to the older, more commonly prescribed medications (VPA, CZP), and to 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 sample size is limited. A multicenter prospective study is needed to draw more definitive conclusions, including assessing linear patterns of seizure types, and such a study is currently in the early stages.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Questionnaire S1. Epilepsy in Angelman syndrome (AS) questionnaire.

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