

# Behavioral disinhibition and antiepileptic treatment in childhood epilepsy: A retrospective cohort study

\*Diana C. van Tuijl, †Rolf H. H. Groenwold, \*Chantal Vlaskamp, ‡§Jolien S. van Campen, ‡Kees P. J. Braun, ‡Floor E. Jansen, and \*Hilgo Bruining

*Epilepsia Open*, 2(1):59–66, 2017

doi: 10.1002/epi4.12032

## SUMMARY

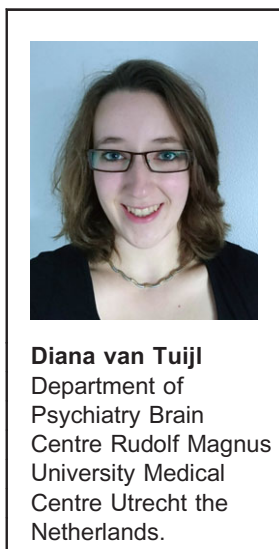
**Objective:** To test whether specific classes of antiepileptic drugs increase the risk for behavioral disinhibition, a frequent complication of treatment of childhood epilepsy.

**Methods:** In a sample of children with active epilepsy and antiepileptic drug (AED) treatment ( $n = 146$ , age 4–17 years), we performed a retrospective chart analysis of the occurrence of symptoms indicating reduced behavioral disinhibition following AED treatment. We used a risk-set approach to analyze whether the presence or recent addition of AED categories defined by their mechanism of action were associated with enhanced risk for behavioral disinhibition symptoms.

**Results:** Mean duration of follow-up was 2,343 days (range 218–6,292, standard deviation [SD] 1,437). Episodes of behavioral disinhibition were reported in 51 (34.9%) children, with variable latencies between latest change and occurrence of behavioral disinhibition symptoms (mean 67 days, range 2–367). Current use of AEDs targeting gamma-aminobutyric acid (GABA) (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.02–3.29,  $p = 0.04$ ) and SV2A-mediated neurotransmitter release (SV2A)-mediated (2.0, 1.13–3.60,  $p = 0.02$ ) neurotransmitter release was associated with increased risk for behavioral disinhibition. Restricting the analysis to the 90 days before behavioral disinhibition episode occurrence revealed that only addition of GABAergic AEDs (OR = 26.88, 95% CI = 6.71–107.76,  $p < 0.001$ ) was associated with behavioral disinhibition. In contrast to our expectations, seizure control was reported to have improved parallel to most behavioral disinhibition episodes.

**Significance:** This exploration of behavioral disinhibition in relation to antiepileptic drug treatment indicates that GABA potentiating drugs are specifically associated with behavioral problems during treatment of childhood epilepsy. Behavioral disinhibition episodes often occurred while seizure control improved, which may have reduced alertness for the consequences of AEDs on interictal symptoms. Our findings may be related to the increasing evidence for a role for excitatory actions of GABA in childhood epilepsy.

**KEY WORDS:** Epilepsy, Behavioral disinhibition, GABA, Antiepileptic drugs.



Childhood epilepsy (CE) is a common and dynamic neurological disorder affecting 0.5–1% of children,<sup>1</sup> with seizure control as the primary treatment target. Comorbid

cognitive and behavioral disorders are strongly associated with CE<sup>2</sup> and cause a major burden, which is often under-recognized.<sup>3</sup> Intrusive behavioral symptoms such as

Accepted November 19, 2016.

\*Department of Psychiatry, Brain Centre Rudolf Magnus, University Medical Centre, Utrecht, the Netherlands; †Julius Centre, University Medical Centre, Utrecht, the Netherlands; ‡Department of Pediatric Neurology, Brain Centre Rudolf Magnus, University Medical Centre, Utrecht, the Netherlands; and §Department of Psychiatry, Radboudumc, Nijmegen, the Netherlands

Address correspondence to Hilgo Bruining, Department of Psychiatry KC03.063.0, University Medical Centre, PO Box 85090, 3508 AB Utrecht, the Netherlands. E-mail: h.bruining@umcutrecht.nl

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## KEY POINTS

- GABAergic drugs can trigger behavioral disinhibition in childhood epilepsy
- Behavioral disinhibition can occur independent of seizure control in children
- Further studies are needed to show whether depolarizing GABA may contribute to drug-induced behavioral disinhibition

irritability and aggression often accompany CE and can severely undermine daily functioning.<sup>4,5</sup> The mechanism behind behavioral problems in CE is largely unclear. The occurrence of behavioral problems is generally attributed to various factors such as the neuropathology of epileptic syndromes, functional damage following seizures, and comorbid developmental disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD).<sup>2–5</sup>

Behavioral symptoms can emerge or become aggravated later in the course of the disease.<sup>4</sup> As a consequence, several antiepileptic drug (AED) treatments have been associated with negative effects on behavioral functioning and control. Levetiracetam is well recognized for causing symptoms of mood instability, aggression, and irritability.<sup>6–8</sup> Another well-known example is adverse behavioral response to AEDs such as barbiturates and benzodiazepines, compounds that enhance GABAergic signaling. This type of (sub)acute induced loss of behavioral control is generally referred to as (paradoxical) disinhibition.<sup>9–12</sup> This well-known clinical symptom has recently received renewed attention. The conventional hypothesis in CE has been that hyperexcitability and seizures are related to a reduction of GABAergic inhibition. This view has been challenged by the finding that the nature of gamma-aminobutyric acid (GABA) transmission is not always inhibitory but can also be excitatory.<sup>13</sup> This polarity of GABAergic transmission depends on the intracellular concentration of chloride in the postsynaptic neuron. In several forms of CE, a depolarizing effect of GABAergic stimulation has been suggested as a source of hyperexcitability, which may have repercussions for AED treatment practice. When GABA stimulation lowers the threshold for generating action potentials, GABA potentiating drugs will not reduce but augment hyperexcitability.<sup>14,15</sup> Apart from an effect on seizures, stimulatory GABAergic AED effects can also be expected to have behavioral consequences reminiscent of paradoxical behavioral disinhibition.

Here, we hypothesized that AEDs that enforce GABAergic signaling are associated with increased risk for symptoms indicating reduced behavioral control and disinhibition such as irritability, anger, and distractiveness.<sup>12,16,17</sup> To test this hypothesis, we evaluated the clinical

history of behavioral disinhibition symptoms in relation to AED changes in a sample of CE. We performed a risk-set analysis to assess whether the risk for symptoms indicating behavioral disinhibition was increased by the presence or addition of particular AED categories<sup>8</sup> and investigated how behavioral disinhibition symptom occurrence was related to seizure control.

## METHODS

### Study design and participants

We reviewed the medical charts of children, aged 4–17 years, with active epilepsy (i.e., a definitive clinical diagnosis of epilepsy and seizures within 1 year prior to data collection), who consulted the pediatric neurology outpatient clinic of the University Medical Centre Utrecht between September 2012 and April 2015. The same cohort was recently studied on sensory modulation problems in CE.<sup>18</sup> In this questionnaire study, responsive caregivers had provided additional information about the age of seizure onset, current seizure frequency, current use of medication, and comorbidities, including a detailed account of previous and family psychiatric diagnoses and/or symptomatology. For this study, we additionally made a detailed chart inventory of the course of AED regimes in each patient during his or her follow-up at the outpatient pediatric neurology clinic of the UMC Utrecht. For each change in AED regime, we extracted the reason for change and its effect on behavior and seizure severity and frequency. Results of neuropsychological tests, previously obtained by van Campen et al.,<sup>18</sup> were evaluated for full-scale intelligence quotient (IQ) or developmental quotient (DQ, also known as mental developmental index [ $\text{Mental age} \div \text{Calendar age} \times 100$ ]), both referred to as “intelligence.” In addition, we extracted information about age of seizure onset, localization of epileptiform activity, etiology (according to the proposed terminology by the International League Against Epilepsy in 2010),<sup>19</sup> earlier diagnostic specialist reports of ASD or ADHD, and current behavioral problems.

### Variables

In line with previous studies on drug-induced paradoxical behavioral disinhibition,<sup>12,16,17</sup> we conceptualized behavioral disinhibition as the loss of some form of (social) behavioral control and respectively classified the following symptoms as possible behavioral disinhibition symptoms: increased talkativeness, emotional release, excitement, excessive movement, and hostility and rage. The following formal criteria were applied to arrive at the diagnosis of a behavioral inhibition episode: (1) the behavioral symptoms reported by the treating child neurologist were classified as a behavioral disinhibition symptom episode only when they were explicitly reported as a novel (behavioral) problem in the course of AED treatment, that is, that were not present before the onset of AED treatment, (2) symptoms did not

occur in the context of previously diagnosed mood disorder or anxiety disorder, (3) symptoms were of substantial severity leading to intervention, either in the form of AED regime change or the start of behavioral therapy or medication, (4) symptoms were not clearly related to other attributed factors, such as changes in social environment or hospitalization. AEDs were categorized based on their mechanism of action as previously described by Perucca and Mula.<sup>8</sup> Categories were Na<sup>+</sup>-channel blockade (NAB), Ca<sup>2+</sup>-channel blockade (CAB), modulation of SV2A-mediated neurotransmitter release (SV2A), antagonism of glutamate (AGL), potentiation of GABA activity (GAB), and alpha-2-delta modulation (A2D). It should be noted that some AEDs have multiple targets, and these were therefore counted in multiple categories in the analyses.

### Statistical methods

We used a risk-set approach, because of the dynamic population, the time-dependent nature of exposure (AED), and the onset of behavioral disinhibition.<sup>20,21</sup> This flexible approach allowed us to estimate precise effects of time-dependent exposures, using various exposure definitions. Demographic characteristics of subjects with and without behavioral disinhibition were compared to assess the potential for confounding. Information obtained from the medical charts was used to construct a risk set in the statistical software package R; all other statistical analyses were performed using IBM SPSS Statistics version 20. To analyze risk factors for behavioral disinhibition symptom occurrence, we compared the current (at time of symptom occurrence) AED regime and other patient characteristics of each child with an episode of behavioral disinhibition symptoms to “controls,” all other children in the risk set who were at risk, that is, receiving AED treatment, but not showing behavioral disinhibition symptoms at that moment in time. The chi-square test and Fisher’s exact test were used to access the differences of the categorical variables between behavioral disinhibition cases and controls; the independent samples t test (two-sided) was used to determine differences between continuous variables.

We determined the association between the category of current AED use in patients with occurrence of behavioral disinhibition episodes versus current AED use in controls through conditional logistic regression analysis, which estimates odds ratios (ORs) and their 95% confidence intervals (CIs). Using the same analysis, we tested the association between last-added AED category and the occurrence of behavioral disinhibition episodes. In case of a concomitant addition of AED, the case was included in multiple groups on the basis of mechanism of action of the AEDs. OR for behavioral disinhibition symptom episode occurrence was also determined for age, sex, ASD diagnosis, and ADHD diagnosis to test whether these factors influenced behavioral disinhibition occurrence irrespective of AED regime. Statistical analysis was performed blinded to group membership.

Statistical significance for all analyses was defined as  $p < 0.05$ .

## RESULTS

### Participants and descriptive data

From the 158 children with active CE previously included by van Campen et al.,<sup>18</sup> 12 children were excluded because they were not treated with AEDs ( $n = 2$ ) or medical chart information was incomplete ( $n = 10$ ). The reviewed consultation history ranged from December 1997 until April 2015. The mean duration of total follow-up in our outpatient pediatric neurology clinic per individual was 2,343 days (range 218–6,292, standard deviation [SD] 1,436.6). AEDs targeting GABA activity (GAB) and Na<sup>+</sup>-channel blockade (NAB) were prescribed most frequently, both about three times as frequently as AEDs targeting Ca<sup>2+</sup>-channel blockade (CAB), modulation of synaptic vesicle protein 2A-mediated neurotransmitter release (SV2A), and antagonism of glutamate (AGL); AEDs targeting alpha-2-delta (A2D) modulation were prescribed incidentally (Table 1). Rescue medication was not included in the analyses.

### Outcome data

Sixty-three episodes of behavioral disinhibition symptoms occurred in 51 children (34.9%), of which 14 episodes followed the first AED treatment (monotherapy). Nine episodes occurred in the context of single AED treatment (monotherapy) later on during treatment versus 28 episodes during treatment with multiple AEDs (polytherapy). Eleven (21.6%) children had more than one episode of behavioral disinhibition symptoms (range 2–3). In all analyses, we included only the first episode of behavioral disinhibition symptoms of each child. No differences in age, age of seizure onset, ASD or ADHD diagnosis, IQ, etiology, or localization of epilepsy were observed between behavioral disinhibition cases and cases without behavioral disinhibition (Table 2). In 23 of 51 cases with a behavioral disinhibition episode, specific reference was made to an AED change in response to the behavioral effects. The majority of these changes were to an AED of the NAB category, after which behavioral disinhibition symptoms were noted to persist in only 1 case. In 4 cases, GAB AEDs were switched for another GAB-targeting AED, leading to persistence of behavioral disinhibition symptoms in 3 cases. In the 2 remaining cases, an AGL AED was installed, after which no further behavioral disinhibition symptoms were noted. In the other 28 cases with behavioral disinhibition episodes, no AED change was noted because the adverse effects were accepted because seizure control was obtained parallel to the occurrence of the behavioral disinhibition symptoms or the reason for no change in AED was unclear. The effect of AED treatment on seizure control during the behavioral disinhibition episodes was variable, and most episodes did

Table 1. Prescription frequencies for type and mechanism of action of AEDs

	AED category						Total prescribed
	A2D	AGL	CAB	GAB	NAB	SV2A	
Benzodiazepines				X			144
Carbamazepine							66
Ethosuximide			X				26
Felbamate		X		X	X		10
Gabapentin	X						3
Lacosamide					X		9
Lamotrigine		X	X		X		67
Levetiracetam						X	106
Oxcarbazepine					X		58
Phenobarbital				X			29
Phenytoin					X		38
Pregabalin	X						1
Rufinamide					X		11
Stiripentol				X			8
Topiramate		X		X	X		39
Valproate				X			128
Vigabatrin				X			23
Zonisamide			X		X		11
Total prescribed	4	116	104	381	309	106	

Mechanism of action: A2D, alpha-2-delta modulation; AGL, antagonism of glutamate; CAB, Ca<sup>2+</sup>-channel blockade; GAB, potentiation of GABA activity; NAB, Na<sup>+</sup>-channel blockade; SV2A, modulation of SV2A-mediated neurotransmitter release. Several AEDs have multiple targets. *Total prescribed* refers to incidences of ever prescribed across the sample. Benzodiazepines include clobazam, clonazepam, midazolam infusion, and nitrazepam. Rescue medication was not included.

Table 2. Demographic features in relation to behavioral disinhibition symptom episode occurrence

Characteristics	All children (n = 146)	Children with behavioral disinhibition (n = 51)	Children without behavioral disinhibition (n = 95)	p value
Sex: boys (n, %)	76 (52.1)	26 (51.0)	50 (52.5)	0.86
Age at first consultation evaluated	137.68 ± 43.42	137.68 ± 41.91	137.26 ± 44.43	0.64
Age at seizure onset ± SD (months)	51.9 ± 49.0	49.3 ± 48.6	53.4 ± 49.4	0.64
Intellectual disability (IQ < 70) (n, %)	57 (39.0)	19 (37.3)	38 (40.0)	0.86
Total (estimated) IQ score ± SD	78.1 ± 23.6	78.9 ± 21.2	77.7 ± 24.9	0.76
Neonatal seizures (n, %)	8 (5.5)	2 (3.9)	6 (6.5)	0.71
Etiology				
Genetic (n, %)	16 (11.0)	6 (11.8)	10 (10.5)	0.79
Structural (n, %)	72 (49.3)	23 (45.1)	49 (51.6)	0.49
Metabolic (n, %)	7 (4.8)	5 (9.8)	2 (2.1)	0.05
Unknown (n, %)	51 (34.9)	17 (33.3)	34 (35.8)	0.86
Localization, lobe				
Frontal (n, %)	29 (19.9)	12 (23.5)	17 (17.9)	0.51
Temporal (n, %)	28 (19.2)	12 (23.5)	16 (16.8)	0.38
Parietal (n, %)	9 (6.2)	6 (11.8)	3 (3.2)	1.00
Occipital (n, %)	9 (6.2)	5 (9.8)	4 (4.2)	0.28
ADHD				
Diagnosis (chart-based) (n, %)	8 (5.5)	5 (62.5)	3 (37.5)	1.00
ASD				
Diagnosis (chart-based) (n, %)	21 (14.4)	13 (61.9)	8 (38.1)	0.81

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; SD, standard deviation.



not concur with aggravation of seizures characterized by increase in frequency and/or severity (Fig. 1).

### Main results

The risk-set approach was first used to compare the presence of AEDs among the regimes of behavioral disinhibition cases to cases without behavioral disinhibition at the time point of consultation for behavioral disinhibition. Analysis of current AED regimes showed that current use of SV2A (i.e., levetiracetam) and GAB-targeting AEDs was associated with an increase in risk for behavioral disinhibition symptom episodes (Table 3). The risk for a behavioral disinhibition episode was not related to current use of the other AED categories (NAB, CAB, and AGL). No association between odds ratio (OR) for behavioral disinhibition symptom occurrence and age, sex, ASD or ADHD diagnosis, or epilepsy etiology was found (data not shown).

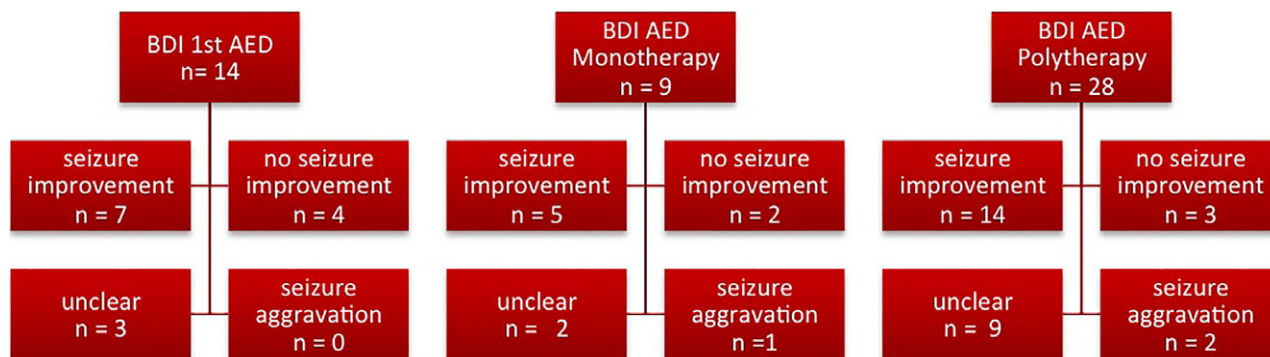
Analysis of the last-added AED in relation to the occurrence of behavioral disinhibition symptom episodes showed that the mean time between initiation of last-added AED and indicated onset of behavioral disinhibition symptoms was variable (mean 67 days, range 2–367 days). To increase the likelihood that a behavioral disinhibition episode was potentially an effect of the last-added AED related to behavioral disinhibition, we chose to restrict the period between AED change and reported behavioral disinhibition episode onset to 120 days, thereby including the majority of the cases of behavioral disinhibition episodes (Table 3). In 9 cases, the latency was <14 days, in 9 <30 days, in 12 <90 days, and in the remaining 9 cases this latency was longer than 120 days.

Occurrence of behavioral disinhibition was associated with last addition of GAB AED categories and tended to be associated with last addition of levetiracetam (Table 3). The OR for last addition of NAB, CAB, and A2D categories could not be calculated (or was zero) because no AEDs of these categories had been added as the last AED prior to

onset of behavioral disinhibition symptoms in children on polytherapy nor were these AED types among first AED or monotherapy regimes. It should be noted that other AED categories than GAB or SV2A AEDs had been frequently used as first AEDs in cases *without* behavioral disinhibition episodes, most notably NAB AEDs in 27 of the 95 non-behavioral disinhibition cases (28.4%). When expanding the analyses to any latency between AED initiation and behavioral disinhibition episode occurrence, we found a trend significant association for GAB AED category as the last-added AED class (OR = 1.97, 95% CI = 0.92–4.25,  $p = 0.08$ ) (Table 3).

## DISCUSSION

Our results indicate that GABA-targeting AEDs are specifically associated with an increased risk for disruptive symptoms indicating reduced behavioral control or inhibition, here referred to as behavioral disinhibition, in childhood epilepsy. Using a dynamic risk-set approach on information obtained from medical chart review, we found that AEDs from the GAB and SV2A (i.e., levetiracetam) category were associated with episodes of behavioral disinhibition symptoms. In support of this association, no use of other AED categories than GABA and SV2A was found among first AED or monotherapy AED in cases *with* behavioral disinhibition episodes, whereas, for instance, NAB-targeting AEDs were common as first AED in cases *without* behavioral disinhibition episodes. Substitution for non-GAB AEDs generally resulted in cessation of behavioral disinhibition symptoms, whereas substitution for other GAB AEDs led to their persistence in some cases. An important observation was that behavioral disinhibition symptom episode occurrence was not accompanied by reduced seizure control in most cases. In fact, seizure frequency or severity often improved while behavioral disinhibition symptoms occurred. To our knowledge, this is the



**Figure 1.**

Relation of BDI symptom occurrence to seizure control. BDI 1st AED refers to BDI symptoms occurring after initiation of the first singular AED at disease; BDI AED monotherapy and AED polytherapy refers to BDI episode occurring parallel to use of singular or multiple AED respectively. Seizure improvement refers to either reduction in seizure frequency and/or severity. Unclear refers to missing or incomplete reports on the concomitant effect of AED regimes on seizure control during the BDI symptom episode occurrence

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**Table 3. Risk-set approach analysis outcomes for current AEDs and last-added AED**

	Current use			Last-added AED within 90 days prior to behavioral disinhibition		
	OR	95% CI	p value	OR	95% CI	p value
NAB	1.35	0.74–2.47	0.33	NP	NP	NP
CAB	0.53	0.19–1.48	0.22	NP	NP	NP
SV2A	2.02	1.13–3.60	0.02	7.70	0.98–60.09	0.05
GAB	1.84	1.02–3.29	0.04	26.88	6.71–107.76	<0.001
AGL	1.26	0.44–3.59	0.67	3.51	0.36–34.42	0.28
A2D	NP	NP	NP	NP	NP	NP

A2D, alpha-2-delta modulation; AGL, antagonism of glutamate; CAB, Ca<sup>2+</sup>-channel blockade; CI, confidence interval; GAB, potentiation of GABA activity; NAB, Na<sup>+</sup>-channel blockade; NP, not prescribed; OR, odds ratio; SV2A, modulation of SV2A-mediated neurotransmitter release. The OR for current use of A2D could not be calculated because no cases were using this AED category at the time of behavioral disinhibition symptom occurrence.

OR, odds ratio of the presence versus absence of AED category in cases with behavioral disinhibition symptoms compared to all subjects with no behavioral disinhibition at that time point.

first study to investigate behavioral effects of combined AED categories based on their assumed mechanism of action. The drugs that we collectively categorized<sup>8</sup> under GAB-targeting AEDs have various mechanisms to enhance GABAergic signaling. The postsynaptic effect, however, of all GAB drugs on GABA transmission is related to chloride levels in the target cells. Paradoxical behavioral disinhibition following benzodiazepines and barbiturates is a well-known phenomenon, both in clinical and nonclinical populations.<sup>10,12,17,22–24</sup> AEDs that are stated to have mood-stabilizing effects include topiramate and valproate,<sup>6</sup> both GAB AEDs. Interestingly, 12 of the behavioral disinhibition cases were reported after initiation of use of topiramate (n = 1) and valproate (n = 11). Although effect on behavioral disinhibition symptoms could not be indicated for A2D AEDs, possible effects could not be ruled out because effect of A2D on GABA transmission is controversial.<sup>8</sup> The principal SV2A-targeting AED, levetiracetam, has previously been marked as an AED with adverse effects related to behavioral disinhibition, for example, irritability and anger.<sup>25,26</sup> Accounts of other AEDs causing reduced behavior or seizure control have been made (e.g., see references 27–30), but to our knowledge, no studies have investigated behavioral effects on the basis of the mechanism of action of AEDs. Overall, our findings indicate that GAB- and SV2A-targeting AEDs increase the risk for behavioral disinhibition symptoms without a similar evident negative effect on seizure control.

The main attributed antiepileptic effect of levetiracetam is the neuronal binding to synaptic vesicle protein 2A, but the drug is also known to strengthen GABAergic transmission by stabilizing cortical receptors and opposing negative allosteric GABA modulators.<sup>25,31</sup> We can only speculate whether our observation of increased risk for behavioral disinhibition episodes through GAB AEDs relates to the nature of GABAergic transmission. However, it has become evident that depolarizing GABA contributes to enhanced excitability in persistent immature networks. Furthermore, accumulation of intraneuronal chloride,

caused by recurrent seizures, may also increase excitatory GABA drive in epilepsy syndromes other than neonatal or early onset types.<sup>32</sup> Acquired chloride loading resulting from ongoing seizures has also been suggested to occur when GABAergic interneurons are chronically challenged.<sup>33</sup> Perhaps this could explain delayed intervals between reported onset of behavioral disinhibition episodes, but we acknowledge that other (environmental) factors are also likely to contribute to or trigger the behavioral problems in the course of treatment. The latency between added AED and behavioral disinhibition was variable, possibly explained by a variable clinical follow-up time or recall bias by parents. An alternative explanation for longer latencies is that behavioral symptoms are sometimes attributed to the underlying disease rather than to possible adverse effects of AEDs. Both neurologists and parents may desire seizure control at the cost of behavioral problems.<sup>4</sup> This possibility is likely given our observation that behavioral disinhibition episodes often occurred while seizure control improved. In nearly half of cases with behavioral disinhibition episodes in our sample, improved seizure control was noted, possibly indicating dissociation between positive seizure effects and negative behavioral effects of AEDs. A potentially relevant finding has been described in the context of emergence of psychosis following the establishment of seizure control in uncontrolled epilepsy patients.<sup>34</sup> A recent study of interictal cortical inhibition using transcranial magnetic stimulation in patients with idiopathic generalized epilepsy did find in vivo evidence for excitatory GABA transmission.<sup>35</sup> This might be due to absence of normal developmental maturation of GABA<sub>A</sub> receptor subunits and altered chloride transporter expressions patterns.<sup>36</sup> In keeping with this, the Na-K-Cl cotransporter (NKCC1) antagonist bumetanide can augment phenobarbital (GABA enforcing) anticonvulsive action in different rodent models, including a hypoxic rat model.<sup>37,38</sup> It has recently been shown that bumetanide can prevent seizure emergence in a genetic (KCNQ channel mutation) form of epilepsy.<sup>39</sup>

Previous studies have suggested that paradoxical responses to AEDs may be more frequent among patients with pervasive developmental disorders.<sup>10,24,40</sup> We found no differences in ADHD and ASD diagnoses between behavioral disinhibition cases and controls, suggesting that the mechanisms mediating behavioral disinhibition are not specific for children with both epilepsy and developmental behavioral disorders.

### Limitations

The retrospective analysis of the behavioral effects and indications of AED changes was dependent on the clinical reports of the treating neurologists. Consultations in childhood epilepsy are generally focused on efficacy of AED treatment for seizure control, and behavioral symptoms might have been underreported, especially during relapses of the disease. Recall bias by parents might have occurred. Furthermore, parents might have different standards in accepting or tolerating behavioral problems in view of seizure treatment, potentially resulting in over- or underreporting of behavioral disinhibition symptoms. Because the date of behavioral disinhibition symptom onset is an indicator of the frequency of consultation and report by parents, the analyzed latencies between behavioral disinhibition symptom episode onset and AED change may be subjected to information or recall bias. Despite these limitations, our findings merit further prospective and more rigorously designed research of the relation among behavioral disinhibition, seizure control, and GABAergic stimulation. The complexity of studying behavioral effects of antiepileptic drugs has been extensively reviewed by Eddy et al.<sup>30</sup> This paper also makes valuable recommendations on how more longitudinal studies may be designed to follow up on our current findings.

### CONCLUSION

In this retrospective study, an increased risk for symptoms indicating behavioral disinhibition seems associated with the use or initiation of a GABAergic AED. These findings may be followed up in prospective studies to establish a novel framework for understanding some of the behavioral adverse effects of AEDs.

### FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### DISCLOSURE

None of the authors has any conflict of interest to disclose. No funding was obtained for this study. All authors have no financial relationships relevant to this article to disclose. 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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