Epilessia e disturbi dello spettro autistico
La presa in carico farmacologica

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Epilessia e DSA: le problematiche del trattamento farmacologico

- La scelta del farmaco antiepilettico nel bambino con DSA che sviluppa un'epilessia
- La scelta dello psicofarmaco nel bambino con DSA ed epilessia
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Non esistono trial randomizzati controllati o studi clinici ampi che abbiano testato gli effetti dei FAE in popolazioni ben definite di soggetti con epilessia e DSA

Efficacy spectrum of available AEDs

All seizures & syndromes	All seizures exc. absences	Partial & tonic-clonic	Absences only
Valproic acid	Phenobarbital	Carbamazepine*	Ethosuximide
Benzodiazepines	Primidone	Phenytoin*	
Lamotrigine**		Oxcarbazepine*	
Topiramate (?)		Vigabatrin*	
Felbamate (?)		Gabapentin*	
Zonisamide (?)		Tiagabine*	
Levetiracetam (?)		Pregabalin*	
		Lacosamide	
		Brivaracetam	
		Eslicarbazepine	

*may esacerbate myoclonic and absence seizures; Vigabatrin is also effective in infantile spasms;
** Lamotrigine may aggravate severe myoclonic epilepsy

Table 2. Antiepileptic Drugs (AEDs): Certain Pharmacologic Characteristics and Cognitive and Behavioral Adverse Effect Profile

AED	GABA[a,b]	Glutamate[b,c]	CYP450[d,e]	Metabolism and Elimination	Cognitive AE[f]	Behavioral AE[f]
Benzodiazepines	+		2C19 sub;3A4 sub	Hepatic/renal	+	Sedation, decreased attention, hyperactivity, irritability and aggression
Carbamazepine		+	+ 3A4	Hepatic	+	Affective disorder
Ethosuximide			3A4 sub	Hepatic		Psychosis (forced normalization)
Felbamate	+	+	2E1, 3A4 sub, −2C19, +3A4	Hepatic/renal		Agitation, irritability
Gabapentin			NONE	Renal		Somnolence, aggression, hyperactivity, oppositional
Lamotrigine	+	+	UK	Hepatic		Irritability, anxiety, aggressiveness, hypomania
Levetiracetam	+		NONE	Renal		Somnolence, agitation, aggressive behavior, irritability
Oxcarbazepine		+	+3A4/5, −2C19	Hepatic	+	
Phenobarbital	+		+3A4; Sub 2C9, 2C19, 2E1	Hepatic/renal	+	Hyperactivity, lethargy, irritability, depression
Phenytoin			+ 2B6, 2C9/19 3A4; sub 2C9, 2C19	Hepatic	+	Decreased motor speed, anxiety, aggression, depression
Tiagabine	+		Sub 3A4	Hepatic		Aggression, irritability, lethargy, drowsiness
Topiramate	+	+	+3A4; −2C19	Hepatic/renal	+	Depression, paranoia, acute confusional psychosis
Valproate	+	+	−2C9	Hepatic	+	Encephalopathy, depression
Vigabatrin	+		−2C9	Renal		Sedation, agitation, hyperkinesia, aggression, depression, psychotic symptoms
Zonisamide			Sub 3A4	Hepatic/renal	+	Somnolence, confusion, nervousness, affective problems, psychosis

Modified from Anderson [2004]; Kwan and Brodie [2001]; Mula and Monaco [2009]; Perruca [2005]; Perruca and Meador [2005]; Sankar and Holmes [2004]; and Schmitz [2006]

[a] Increase in GABA levels or potentiation of GABA activity.

[b] Primary or secondary action.

[c] Reduce glutamate mediated excitation.

[d] Cytochrome P450.

[e] +: Inducer, −: inhibitor, ±: inducer and inhibitor, sub: substrate, uk: unknown.

[f] Adverse effects.

(Depositario-Cabacar & Zelleke, 2010)

Epilessia e DSA – Acido valproico

- Diversi report clinici segnalano miglioramenti in bambini che presentano DSA, con o senza crisi, ma con anomalie epilettiformi all'EEG, trattati con VPA (Nass et al., 1990; Plioplys, 1994; Childs & Blair, 1997)
- Un trial in aperto condotto su 14 soggetti trattati con VPA mostra miglioramento dei sintomi "core" dell'autismo, dell'instabilità affettiva, dell'impulsività e dell'aggressività solo nei bambini con autismo, EEG alterato o storia di crisi (Hollander et al., 2001)

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BRIEF REPORT

Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder

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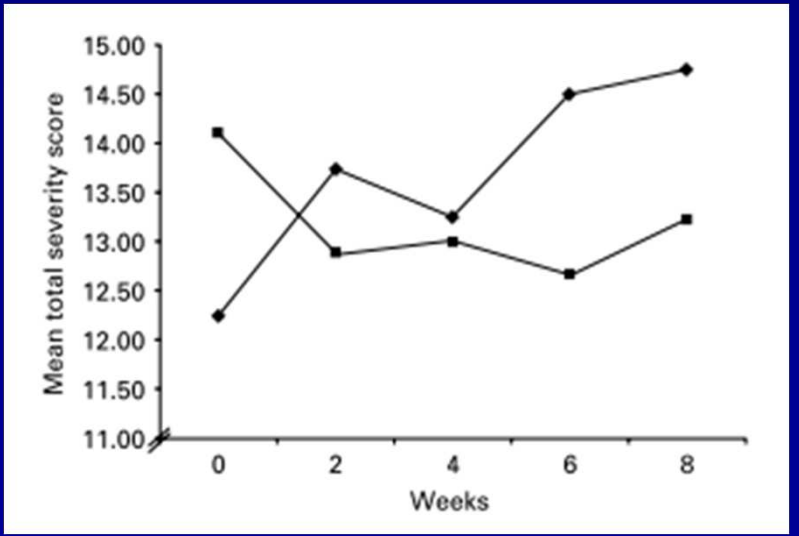
Abstract

Autism is a neurodevelopmental disorder characterized by impairment in three core symptom domains: socialization, communication, and repetitive/stereotyped behaviours. Other associated symptom domains are also affected including impulsivity/aggression, self-injury, anxiety, and mood lability. Divalproex has been shown to have efficacy in treating epilepsy, bipolar disorder, mood lability, and impulsive aggression. The present study evaluated the use of divalproex in the treatment of repetitive, compulsive-like symptoms of autism spectrum disorder (ASD). Thirteen individuals with ASD participated in an 8-wk, double-blind, placebo-controlled trial of divalproex sodium vs. placebo. There was a significant group difference on improvement in repetitive behaviours as measured by the Children's Yale–Brown Obsessive Compulsive Scale (C-YBOCS) ($p = 0.037$) and a large effect size ($d = 1.616$). This study provides preliminary support for the use of divalproex in treating repetitive behaviours in ASD. Further research is needed to evaluate the specificity and mechanism of action of these findings.



ELSEVIER

Antiepileptic Drugs: Affective Use in Autism Spectrum Disorders

Adriana Di Martino, MD* and Roberto F. Tuchman, MD†

Di Martino A, Tuchman RF. Antiepileptic drugs: Affective use in autism spectrum disorders. Pediatr Neurol 2001;25:199-207.

Table 1. Antiepileptics in patients with autism and related conditions

Patient	Age	Diagnosis	Seizure	Abnormal EEG	AED	Epilepsy Control	Behavior Improvement	Reference Citation
3	Child	Asperger ADHD (2) BPD (1)	−	−	VPA	/	+	[21]
2	Child	AUT	−	+	VPA	+	+	[20]
3	Child	AUT	−	+	VPA	?	+	[18]
1	Child	PDD	−	+	VPA	+	+	[15]
2	Child	AUT	−	+	VPA	+	+	[12]
2	Adult	AUT BPD (1) RCD (1)	−	−	VPA	±	+	[14]
1	Child	Asperger	+	+	CBZ	±	−	[19]
2	Child	AUT TS	+ (1)	+	CBZ	+	+	[16]
2	Adolescent	AUT BPD	1+	1+	CBZ	+ (1)	+	[13]
13	Child/adolescent	AUT (12) Rett (1)	+	+	LMG	*	+ (8)	[17]

Epilessia e DSA – Lamotrigina

- In uno studio condotto in bambini con epilessie farmacoresistenti, un sottogruppo di 13 bambini con associato autismo mostra riduzione dei “sintomi autistici”, senza concomitante riduzione delle crisi (Uvebrant e Bauziene, 1994)
- Un successivo trial in DC vs placebo condotto in 28 bambini con autismo e senza crisi non evidenzia significativi miglioramenti degli indicatori comportamentali; i genitori, tuttavia, riferiscono un effetto benefico della lamotrigina (Belsito et al., 2001)

Epilessia e DSA – Levetiracetam

- In uno studio in aperto su 10 bambini con DSA senza epilessia, vengono riferiti effetti positivi su iperattività, impulsività, instabilità dell'umore ed aggressività (Rugino e Samsock, 2002)
- Un secondo studio in 20 bambini con DSA e senza crisi non mette in evidenza effetti positivi sul comportamento (Wasserman et al., 2006)

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A Retrospective
in Childı
with Pervasive

Antonio Y. Hardan, M.D., Ro

An open-label retrospective study wa
of topiramate in children and adoles
Topiramate is a novel antiepileptic dr
orders. A retrospective chart review
treating individuals with developmer
with PDD who received topiramate.
mained unchanged. Treatment respor
the Clinical Global Impressions scale
Conners Parent Scale (CPS), as comp
male, 3 female; age = 14.7 ± 3.3 years)
with Asperger's disorder, and 2 pati
Eight patients (4 patients with autistic
tients with PDD, NOS) were judged
CGI-GI. Treatment duration was 25
ferences between baseline and the e
subscales: conduct, hyperactivity, and
somatic, learning, and anxiety subsca
side effects, with 2 patients experienc
iramate may be beneficial for treatin
label studies and double-blind, placel
needed.

ELSEVIER

Topiramate in children

Dear Sir,

Recurrent aggressior
are a common reason c
logical treatment amon
Disorders (ASD). In th
psychotics and sedative
able results. Drug-indu
drawback for a number
(TPM) is an anticonvu
used also in the treatı
The fact that TMP c
weight gain makes it a
when there is concern

In the April 2005 iss
Canitano report on 10
months with TPM to
[3]. Four patients had
while two children cont
over, a positive effect as
the subject who was tre

We would like to dr
results on five boys (age
diagnosis of DSM-IV a
agement of severe beha
Autism Rating Scale an
Schedule were used to a
in verbal children, or t
two patients performed
and three in the modera
mean +/− SD IQ for th
. Two had received at l
chotic and had discontin
cy or development of a

TPM was started at
weeks, followed by i
2-week intervals, up t
(mean TPM dose wa
received add-on SSRI
for obsessive behavior
term therapy with risp
ranged from 10 to 33
8.33 weeks.

Also Topiramate might have some benefit in psychopharmacological treatment of autism

Sir,

Autism is a neurological disorder causing impairment with respect to communication and activities of daily life. Cholinergic drugs (mainly used for patients suffering from Alzheimer's disease), have been reported to have some benefit in treating patients suffering from autism. Chez et al. [1] published an open-label study demonstrating that Rivastigmine leads to gains in overall autistic behavior and expressive speech. Hertzmann [2] report improvements in verbal fluency, caused by another acetylcholinesterase inhibitor, Galantamine, but also mention verbal and behavioural regression when the patient was on Donepezil, another cholinergic drug. One of our recent observations [3] suggested, that also glutamate antagonists such as the *N*-methyl-D-aspartate glutamate receptor antagonist Memantine may slightly improve some cardinal symptoms in autistic patients, mainly those who are related to irritability and hyperactivity. Because of its adverse side effects (dizzyness, somnolence, headache, hallucinations, hypertension) it should be used with caution. For that reason, it seems to useful to look for substances with fewer side effects, acting similarly. Topiramate, an inhibitor of the excitotoxin kainite, mainly used for treating epilepsy, and administered at an dosage of not more than 50 mg daily, has been reported to have similar side effects, but less marked. Mainly cardiovascular side effects such as hypertonia have not been described in patients medicated with Topiramate. We assume, that Topiramate may also be effective treating autism, but with less probable side effects. We recommend to investigate this substance for the indication ''autism''.

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Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder

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ABSTRACT

Background: Autism is a complex neurodevelopmental disorder that forms part of a spectrum of related disorders referred to as Autism Spectrum Disorders. The present study assessed the effects of topiramate plus risperidone in the treatment of autistic disorder.

Method: Forty children between the ages of 4 and 12 years with a DSM IV clinical diagnosis of autism who were outpatients from a specialty clinic for children were recruited. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated to topiramate + risperidone (Group A) or placebo + risperidone (Group B) for an 8-week, double-blind, placebo-controlled study. The dose of risperidone was titrated up to 2 mg/day for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. The dose of topiramate was titrated up to 200 mg/day depending on weight (100 mg/day for <30 kg and 200 mg/day for >30 kg). Patients were assessed at baseline and after 2, 4, 6 and 8 weeks after starting medication. Measure of outcome was the Aberrant Behavior Checklist-Community (ABC-C) Rating Scale.

Results: Difference between the two protocols was significant as the group that received topiramate had a greater reduction in ABC-C subscale scores for irritability, stereotypic behavior and hyperactivity/noncompliance.

Conclusion: The results suggest that the combination of topiramate with risperidone may be superior to risperidone monotherapy for children with autistic disorder. However the results need to be further confirmed by a larger randomized controlled trial.

Table 2
Mean ± SD of the two protocols on the five subscales of Aberrant Behavior Checklist-Community (ABC–C) rating scale.

Subscales	Week 0	Week 2	Week 4	Week 6	Week 8	Drugs × time interaction
Irritability						
Risperidone + Topiramate [mean (SD)]	17.25 (3.12)	16.40 (3.42)	14.40 (2.89)	12.25 (2.40)	8.20 (2.44)	P = 0.04
Risperidone + placebo [mean (SD)]	16.80 (4.22)	16.65 (4.40)	16.35 (4.92)	15.85 (4.97)	15.30 (4.64)	
Lethargy/social withdrawal						
Risperidone + Topiramate [mean (SD)]	17.65 (6.02)	16.80 (6.16)	16.30 (6.30)	15.25 (6.36)	14.15 (6.67)	P = 0.70
Risperidone + placebo [mean (SD)]	17.55 (4.28)	16.75 (4.11)	16.60 (3.96)	16.15 (4.42)	15.60 (4.28)	
Stereotypic behavior						
Risperidone + Topiramate [mean (SD)]	8.83 (3.89)	7.79 (3.26)	6.90 (2.73)	5.55 (1.82)	3.40 (1.04)	P = 0.04
Risperidone + placebo (mean ± SD)	8.71 (3.21)	8.43 (3.15)	8.07 (2.95)	8.05 (2.94)	8.09 (3.04)	
Hyperactivity/noncompliance						
Risperidone + Topiramate [mean (SD)]	22.75 (4.85)	21.00 (4.7)	17.05 (3.47)	13.50 (3.25)	7.60 (2.37)	P = 0.04
Risperidone + placebo [mean (SD)]	22.00 (9.17)	21.20 (8.59)	20.40 (8.35)	19.70 (8.06)	19.25 (8.30)	
Inappropriate speech						
Risperidone + Topiramate [mean (SD)]	5.25 (2.01)	5.00 (1.93)	4.82 (1.84)	4.32 (1.93)	3.93 (2.17)	P = 0.98
Risperidone + placebo [mean (SD)]	5.10 (1.80)	4.86 (1.63)	4.56 (1.34)	4.49 (1.53)	4.24 (1.59)	

Oxcarbazepine in Youths With Autistic Disorder and Significant Disruptive Behaviors

SUAD KAPETANOVIC, M.D.
Los Angeles, Calif.

Am J Psychiatry 164:5, May 2007

TO THE EDITOR: Disruptive behaviors are a frequent reason for psychiatric visits among autistic individuals. The following case report describes beneficial effects in three consecutive oxcarbazepine-treated autistic youths with disruptive behaviors. All three patients had been conjointly engaged in behavioral therapies provided by local treatment facilities.

"A.B." is a 13-year-old Hispanic male with frequent aggression toward others and property, irregular sleep, and poor ability to follow instructions. Previous effective trials of risperidone and olanzapine were both discontinued because of elevated liver transaminases and excessive weight gain, respectively. Oxcarbazepine was titrated to 300 mg every morning and 600 mg every night over 7 days. Two weeks later, the patient's mother reported improved compliance at home, and school reports showed improved cooperation and attention span. The aggression was decreased in severity and frequency, and regular sleep was established. He has been stable on this regimen for 4 months.

"C.D." is a 19-year-old Caucasian female with dysfunctional compulsive routines, head banging, and frequent violent outbursts. Fluoxetine was titrated to 20 mg daily over 2 months. The compulsive symptoms improved dramatically, but she remained aggressive. Risperidone augmentation failed, so oxcarbazepine was titrated to 600 mg b.i.d. One month later, her tantrums were significantly reduced, and cooperativeness improved. The head banging was reduced from more than 10 spells per day to approximately once per week. The patient has been on this combination of fluoxetine and oxcarbazepine for 6 months.

"E.F." is a 4½-year-old Hispanic child whose symptoms included head banging, property destruction, hitting others, irregular sleep, and hyperactivity. Previous treatments with methylphenidate and amphetamine salts resulted in agitation; trials of guanfacine and risperidone failed. Oxcarbazepine was titrated to 150 mg every morning and 300 mg every night over 2½ months, resulting in normalized sleep schedule, improved cooperativeness, and lessened aggression. The patient has been maintaining these improvements for 3½ months.

Written informed consent was obtained from the legal guardians in all three cases. None of the patients have developed hyponatremia or other untoward outcomes.

To our knowledge, this is the first report of oxcarbazepine use in autism with disruptive behaviors. These symptoms are best managed by combining behavior modification and psychotropic agents (1). While haloperidol and risperidone have solid evidence base supporting their efficacy and effectiveness in this indication, their side-effect profiles (i.e., extrapyramidal symptoms and weight gain, respectively) are equally well documented (2). Controlled trials also support fluoxetine and fluvoxamine, but treatment-emergent behavioral activation (3) limits their clinical applicability. Oxcarbazepine has a more favorable side-effect profile, and it is available in liquid form, which is often more convenient for autistic patients. Hopefully, this report will inspire future research on the effects of oxcarbazepine in autistic individuals.

ANNALS *of Neurology*

A Novel Hypothesized Clinical Implication of Zonisamide for Autism

Ahmad Ghanizadeh, MD

In an interesting recently published study, Asanuma et al reported that zonisamide, which is used as an antiepileptic medication and a novel antiparkinsonian drug, significantly increases glutathione levels in astroglial cells.[1] Zonisamide enhances cystine/glutamate exchange and increases influx of cystine. Cystine is an important substrate for glutathione synthesis, and glutathione is an antioxidant. Herein, I would like to discuss another possible clinical and research implication of their findings.

Autism is neurodevelopmental disorder, the prevalence of which is rising. Its etiology is not exactly known, and there is no curative treatment. Methionine, cystine, and glutathione concentration in children with autism were found to be lower than in a control group,[2] whereas a higher concentration of oxidized glutathione was reported in children with autism.[2] This lower methionine concentration is due to reduction in methionine synthase activity.[2] A consequence of decreased methionine cycle turnover is decrease of cystine and glutathione synthesis.[2] Glutathione is made from cystine, glutamate, and glycine. Cystine has an important role in the synthesis of glutathione, because its concentration is lower than that of glycine and glutamate. Therefore, cystine has a limiting role for glutathione synthesis. One of the sources of cystine is direct import from plasma.[3] Another source of cystine is via methionine cycle.[3] Low cystine concentration decreases glutathione synthesis.[4] The role of glutathione in antioxidant effect is clear in many disorders, such as parkinsonism and autism. Low glutathione increases vulnerability to oxidative stress. Increased oxidative stress and decreased methylation capacity and glutathione concentration contribute to autism clinical manifestation.[2] Demand for cystine, methionine, and glutathione is increased during chronic oxidative stress[4] such as autism. Lower concentration of methionine, cystine, and glutathione is suggested as a metabolic biomarker of autism.[2] Therefore, there is a possibility that providing more cystine increases methionine cycle and glutathione. This can improve antioxidant activity.

Given that methionine, cystine, and glutathione concentration in children with autism is low, oxidative stress in autism is increased, and demand for cystine, methionine, and glutathione during chronic oxidative stress is high.

Regarding zonisamide, which is a safe medication in young children[5] that increases glutathione by increasing the influx of cystine,[1] another implication of their findings[1] is the need to conduct studies for the assessment of the possible efficacy of zonisamide administration for the management of autism. In conclusion, even if zonisamide may impact on other neurotransmitters, and the mechanism by which it works is still not completely understood, the present hypothesis suggests that conducting clinical trials on this matter may be worthwhile.

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Neuroleptic drugs and seizure threshold

clorpromazina, olanzapina, clozapina

aloperidolo

fenotiazine, tioxanteni, risperidone, quietapina, aripiprazolo, ziprasidone

The Use of Psychotropic Drugs in Epilepsy: What Every Neurologist Should Know

Andres M. Kanner, M.D.[1]

SEMINARS IN NEUROLOGY/VOLUME 28, NUMBER 3 2008

DO ANTIDEPRESSANT DRUGS WORSEN SEIZURES?

Thus, what accounts for the perception that antidepressant drugs cause seizures? In fact, there are four antidepressant drugs—maprotiline, amoxepine, clomipramine, and bupropion (in its immediate-release formulation)—that are known to lower the seizure threshold at therapeutic doses, while antidepressants of the tricyclic, SSRI, and serotonin-norepinephrine-reuptake inhibitor (SNRI) families can cause seizures at toxic concentrations. Indeed, a review of the literature of seizures with TCAs in nonepileptic patients identified seizure occurrence in patients who had taken overdoses or who had high serum concentrations because of their propensity to be "slow metabolizers."[33]

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Ranking AEDs for PK Interaction Potential

carbamazepine, phenytoin, barbiturates

valproic acid

rufinamide, felbamate, oxcarbazepine, topiramate, lamotrigine, tiagabine, benzodiazepines, ethosuximide, zonisamide

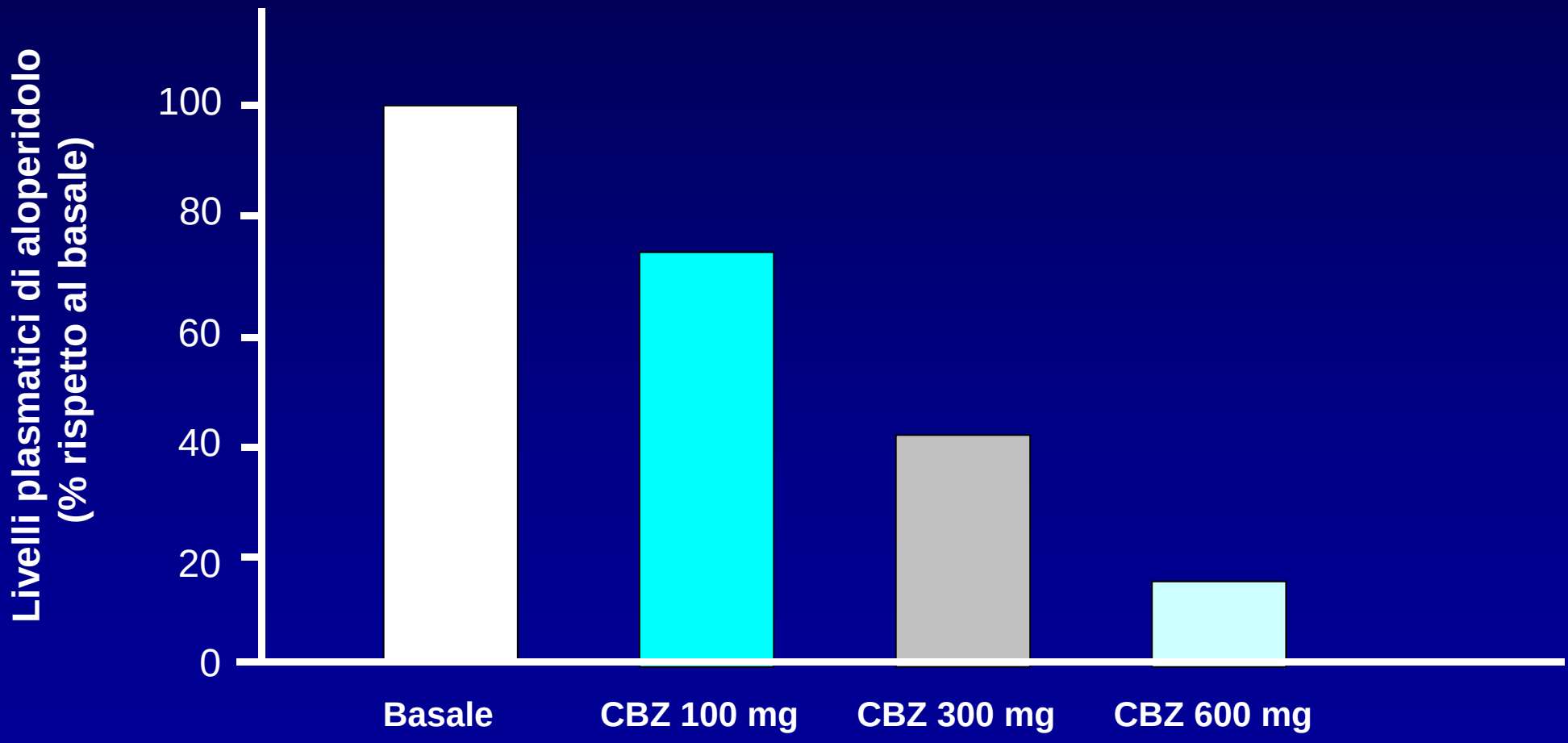
gabapentin, lacosamide, levetiracetam, pregabalin, vigabatrin

Perpetrator and target Target only Little or not involved

Substrati, inibitori ed induttori degli isoenzimi del citocromo P450

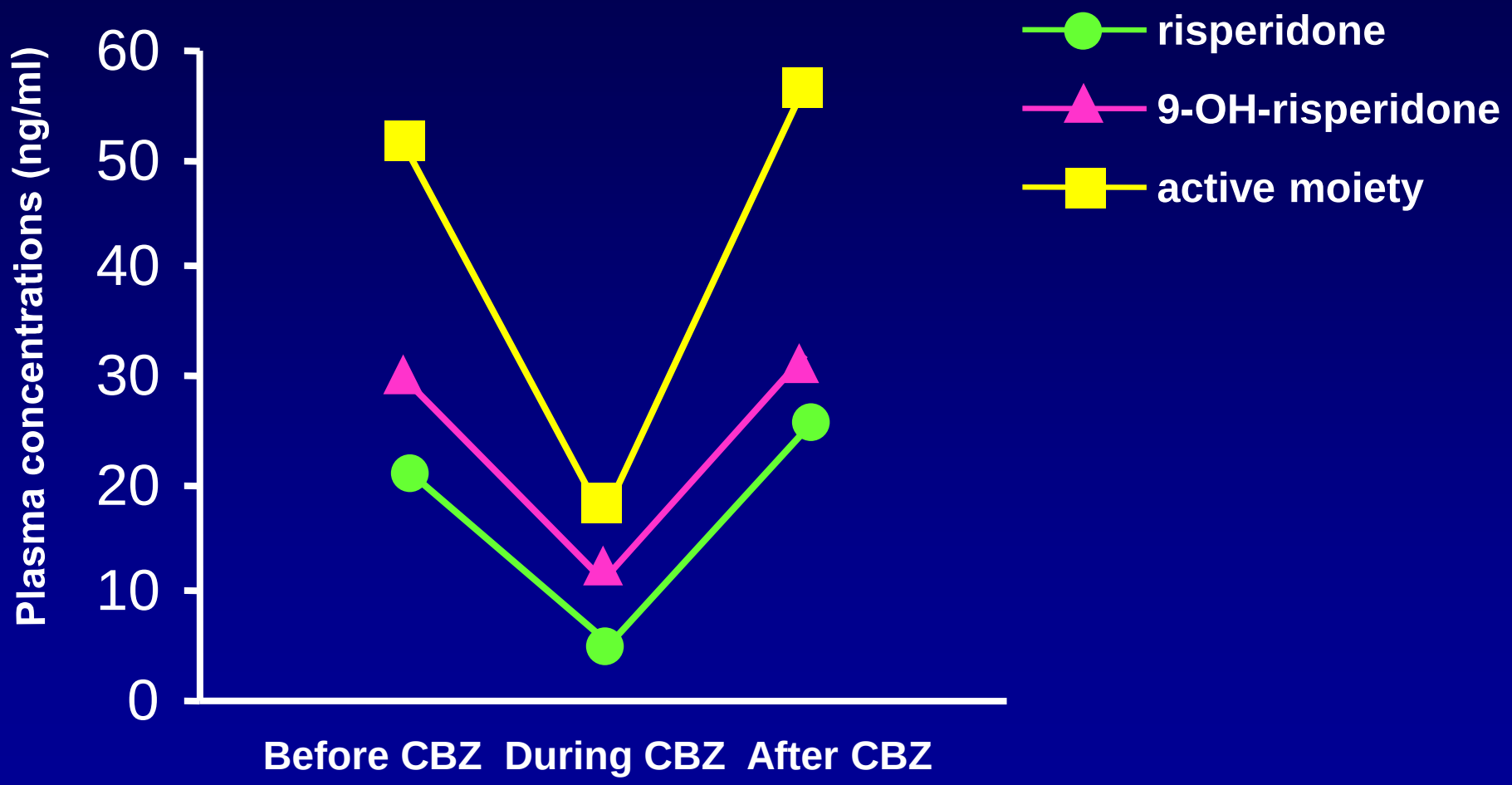
	Farmaci metabolizzati	Inibitori	Induttori
CYP1A2	Antidepressivi: triciclici (demetilazione), fluvoxamina Antipsicotici: clozapina, olanzapina Altri: teofillina, tacrina, propranololo	Fluvoxamina Ciprofloxacina Claritromicina	Carbamazepina Fenobarbitale Fenitoina Fumo
CYP2C9	AEDs: fenitoina, fenobarbitale, acido valproico NSAID: diclofenac, ibuprofene, naprossene, celecoxib Altri: warfarina, tolbutamide, losartan	Amiodarone Fluconazolo Acido valproico Fluoxetina Fluvoxamina	Carbamazepina Fenobarbitale Fenitoina
CYP2C19	AEDs: fenitoina, fenobarbitale Antidepressivi: triciclici (demetilazione), citalopram, moclobemide Altri: diazepam, omeprazolo, propranololo	Omeprazolo Ticlopidina Fluvoxamina	Carbamazepina Fenobarbitale Fenitoina
CYP2D6	Antidepressivi: triciclici (idrossilazione), fluoxetina, paroxetina, venlafaxina Antipsicotici: tioridazina, risperidone, clozapina, olanzapina, aripiprazolo Beta-bloccanti: metoprololo, propranololo, timololo Antiaritmici: encainide, flecainide, propafenone Altri: donepezil, tramadolo	Chinidina Tioridazina Fluoxetina Paroxetina Duloxetina	
CYP3A4	AEDs: carbamazepina, etosuccimide, felbamato, tiagabina, zonisamide Antidepressivi: triciclici (demetilazione), sertralina, reboxetina Antipsicotici: quetiapina, risperidone, aripiprazolo Calcio-antagonisti: diltiazem, felodipina, nifedipina, verapamil Altri: amiodarone, alprazolam, astemizolo, ciclosporina, eritromicina, metadone, etinilestradiolo, levonorgestrel, ritonavir, terfenadina, statine	Ketoconazolo Itraconazolo Eritromicina Troleandomicina Ritonavir Succo di pompelmo	Carbamazepina Fenobarbitale Fenitoina Rifampicina Iperico

Livelli plasmatici di aloperidolo dopo sommistrazione di dosi crescenti carbamazepina in 11 pazienti schizofrenici



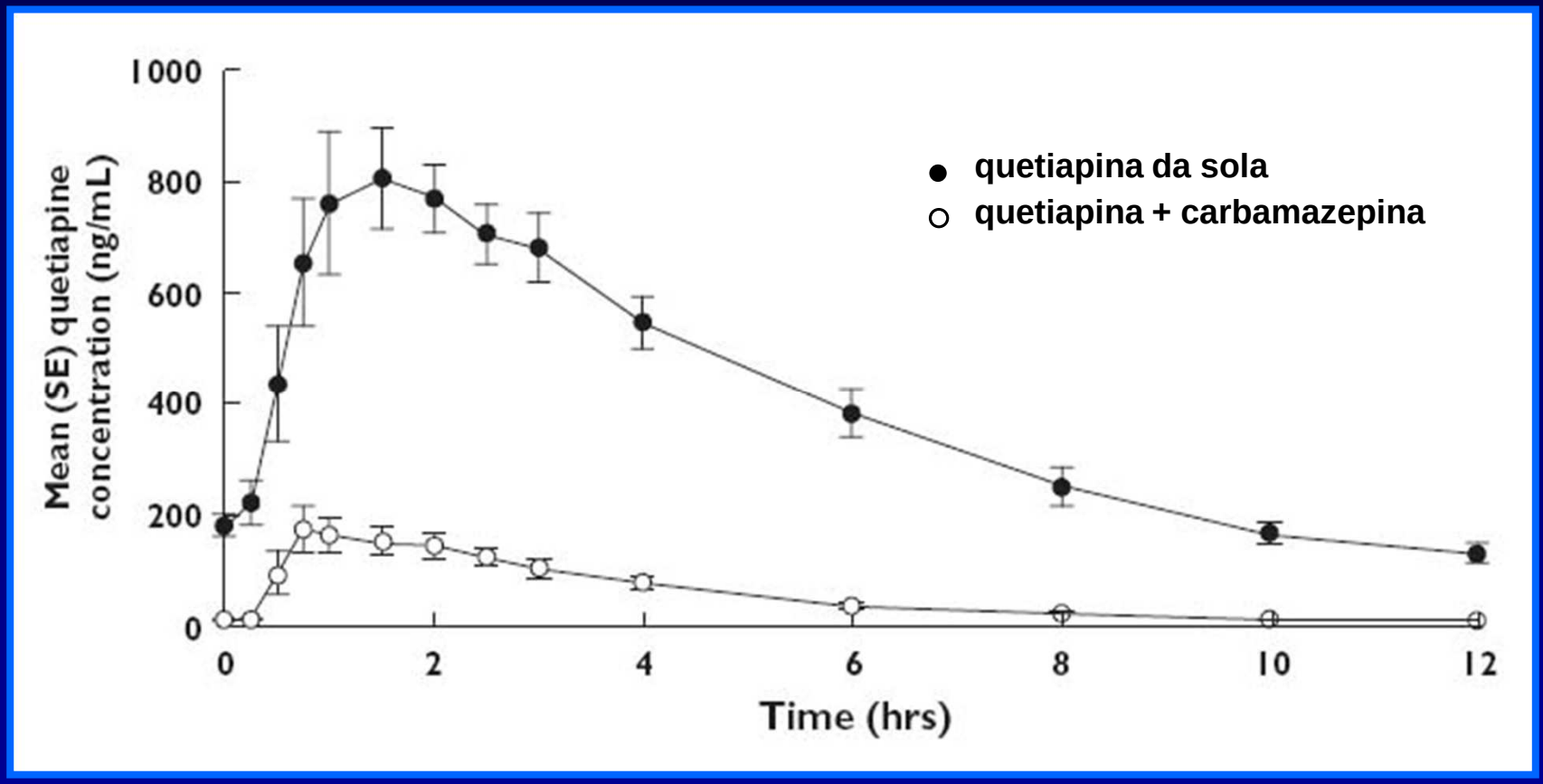
(Yasui-Furukori et al, J Clin Psychopharmacol 2003; 23: 435-440)

Interazione tra carbamazepina e risperidone



(Spina et al., J Clin Psychopharmacol 2001; 21: 108-109)

Interazione tra carbamazepina e quetiapina



(Grimm et al., Br J Clin Pharmacol 2006; 61: 58-69)

Table 3.

Effect of various anti-epileptics on plasma concentrations of novel antipsychotics (only controlled studies are described).

Antiepileptic	Antipsychotic	Effect on plasma concentrations	Proposed mechanism	References	Number of participants, design
Carbamazepine	Clozapine	Decrease (50%)	Induction of CYP1A2, CYP3A4 and UGT	Jerling et al., 1994 [79]	17, parallel, and 8, sequential
				Tiihonen et al., 1995 [111]	12, sequential
	Risperidone	Decrease (50–70%)	Induction of CYP3A4	Spina et al., 2000 [113]	11, parallel, and 5, sequential
			Induction of CYP1A2 and UGT	Ono et al., 2002 [114]	11, sequential
	Olanzapine	Decrease (30–70%)		Olesen & Linnet 1999 [117]	5, parallel
				Linnet & Olesen 2002 [119]	16, parallel
	Quetiapine	Decrease (80%)	Induction of CYP3A4	Skogh et al., 2002 [120]	10, parallel
	Ziprasidone	Decrease (20–40%)	Induction of CYP3A4	Grimm et al., 2005 [121]	18, sequential
				Miceli et al., 2000 [123]	9, sequential
Valproic acid	Clozapine	No change or minimal increase	Enzyme inhibition?	Centorrino et al., 1994 [62]	11, parallel
				Finley & Warner 1994 [124]	4, sequential
				Longo & Salzman 1995 [126]	7, sequential
				Facciolà et al., 1999 [127]	15, parallel, and 6, sequential
	Risperidone	No change		Spina et al., 2000 [113]	10, parallel
	Olanzapine	No change	Enzyme inhibition?	Gex-Fabry et al., 2003 [128]	32, parallel
	Quetiapine	Increase (70–80%)	Protein displacement?	Aichorn et al., 2006 [129]	9, parallel
	Aripiprazole	Decrease (20–30%)		Citrome et al., 2005 [130]	10, sequential
Phenobarbital	Clozapine	Decrease (30–40%)	Induction of CYP1A2, CYP3A4 and UGT	Facciolà et al., 1998 [131]	7, parallel
Phenytoin	Quetiapine	Decrease (80%)	Induction of CYP3A4	Wong et al., 2001 [134]	10, sequential
Lamotrigine	Clozapine	No change		Tiihonen et al., 2003 [140]	34, sequential
				Spina et al., 2006 [141]	11, sequential
	Risperidone	No change		Spina et al., 2006 [141]	10, sequential
	Olanzapine	No change or minimal increase	Competitive inhibition of UGT1A4	Sidhu et al., 2006 [136]	16, sequential
				Jann et al., 2006 [142]	14, sequential
				Spina et al., 2006 [141]	14, sequential
Oxcarbazepine	Risperidone	No change		Muscatello et al., 2005 [143]	12, sequential
	Olanzapine	No change		Muscatello et al., 2005 [143]	13, sequential
Topiramate	Clozapine	No change		Tiihonen et al., 2005 [144]	12, sequential
				Migliardi et al., (in press) [145]	10, sequential
	Olanzapine	No change		Tiihonen et al., 2005 [144]	5, sequential
				Migliardi et al., (in press) [145]	12, sequential
	Risperidone	No change		Migliardi et al., (in press) [145]	9, sequential
	Quetiapine	No change		Migliardi et al., (in press) [145]	7, sequential

Interazioni farmacodinamiche tra FAE e nuovi antipsicotici

	Possibili conseguenze
Carbamazepina + Clozapina	Da evitare per il possibile potenziamento degli effetti ematologici Segnalati casi di sindrome maligna
Valproato + Clozapina	Possibili effetti indesiderati di tipo additivo (aumento di peso, sedazione) Segnalati casi di neurotossicità
Valproato + Olanzapina	Possibili effetti indesiderati di tipo additivo (aumento di peso, sedazione)

Interazioni tra litio e FAE

	Possibili conseguenze
Litio + Carbamazepina	Segnalati casi di neurotossicità, soprattutto in pazienti con pre-esistenti patologie del SNC
Litio + Valproato	Possibili effetti indesiderati di tipo additivo (aumento di peso, sedazione, tremore, turbe gastrointestinali)
Litio + Nuovi AEDs	Non segnalati eventi indesiderati

Epilessia e DSA: le problematiche del trattamento farmacologico

- La scelta del farmaco antiepilettico nel bambino con DSA che sviluppa un'epilessia
- La scelta dello psicofarmaco nel bambino con DSA ed epilessia
- Le interazioni farmacocinetiche e farmacodinamiche tra FAE e farmaci psicotropi
- Il trattamento del bambino con epilessia che sviluppa un DSA (encefalopatia epilettica)
- La gestione del bambino con regressione autistica ed anomalie epilettiformi all'EEG

Encefalopatie epilettiche con rischio di DSA - Trattamento

- **Sindrome di West** → **corticosteroidi (efficacia 70% dei casi), GVG (40-90%), TPM (45%), BZs (20-50%), etc.**
- **Sindrome di Landau-Kleffner** → **corticosteroidi, GVG, STM, CLB, LEV, DZP, Igs, DK, etc.**
- **ESES** → **corticosteroidi (effetto sull'EEG nel 65% dei casi), altre terapie (eff. in < 50% dei casi)**

Epilessia e DSA: le problematiche del trattamento farmacologico

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La regressione autistica è dovuta all'attività EEG epilettiforme, in assenza di crisi cliniche?

No!

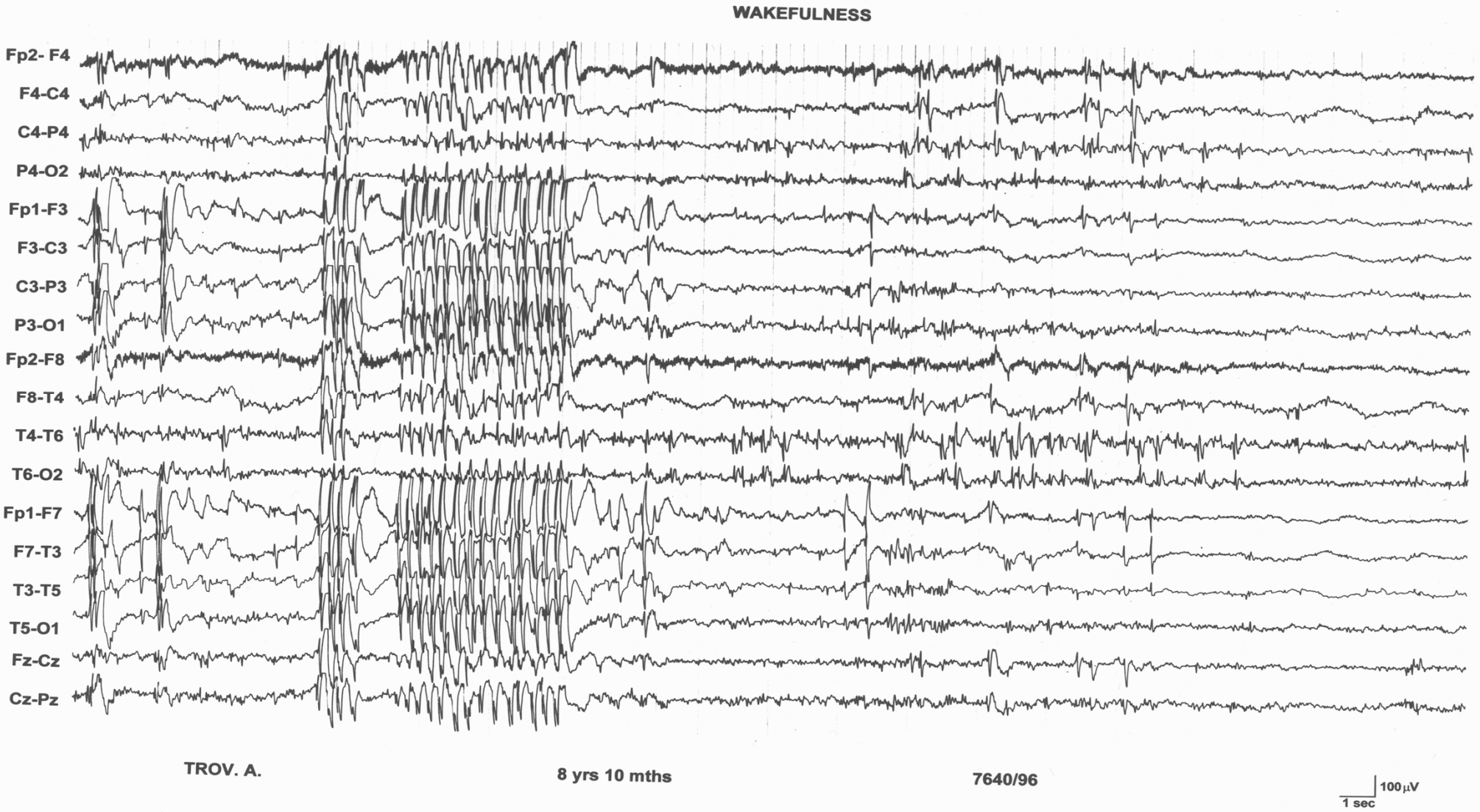
Tuchman & Rapin, 1997

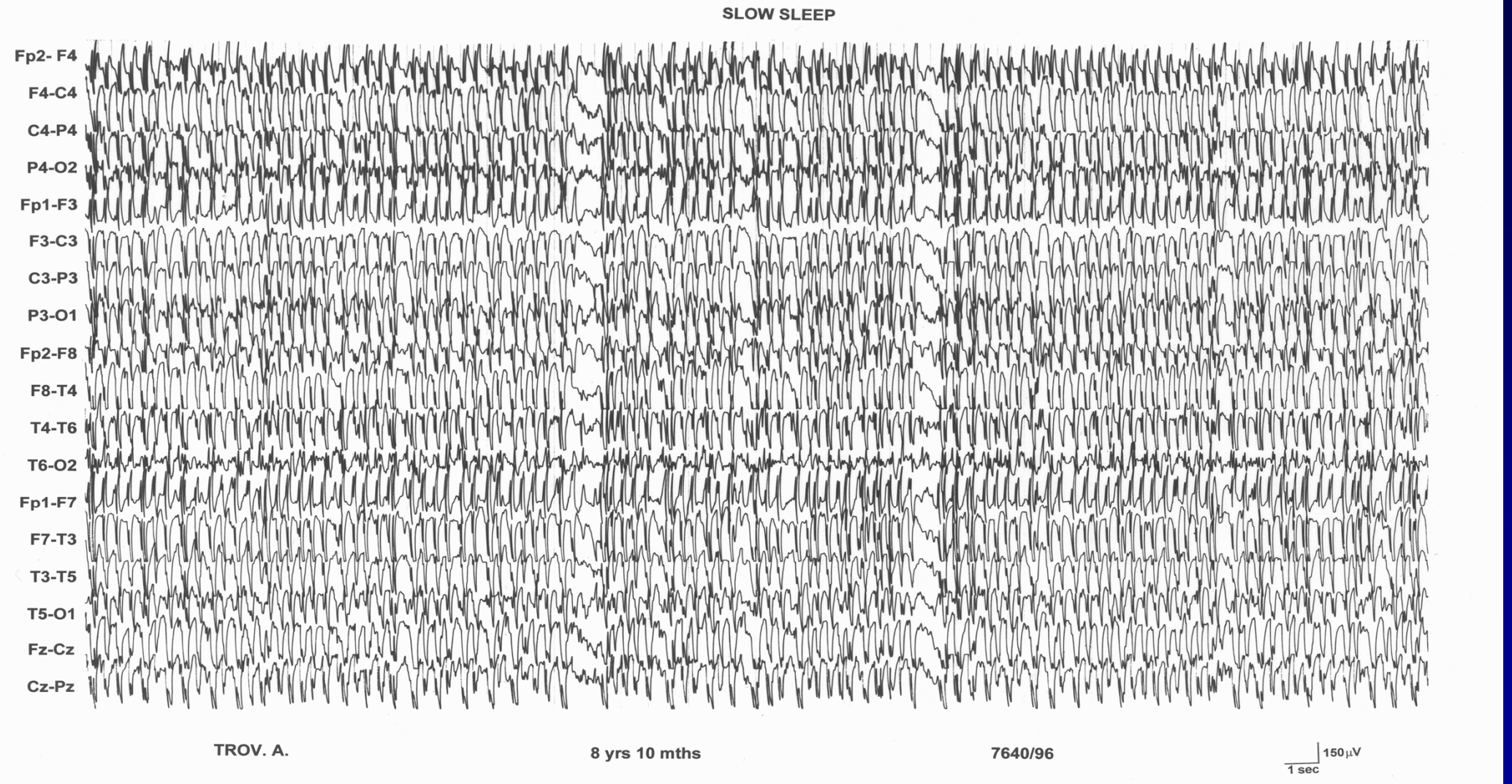
Hrdlicka et al., 2004

Canitano et al., 2005

Chez et al., 2006

Baird et al., 2006


WAKEFULNESS
Fp2- F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
TROV. A.
8 yrs 10 mths
7640/96
100 µV
1 sec


SLOW SLEEP
Fp2- F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
TROV. A.
8 yrs 10 mths
7640/96
150 µV
1 sec

- Currently, there is no evidence in studies of autism of an epileptic encephalopathy analogous to LKS
- So, there is insufficient evidence to prescribe AEDs for subclinical discharges in autism (but see Chez et al., 2006: 80/176 pts, 63.6%, with EA improved or normalized)
- Randomized control trials are needed to monitor both behavioural outcome and EEG picture

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www.elsevier.com/locate/braindev

Review article

Autism spectrum disorders and epilepsy: Moving towards a comprehensive approach to treatment

Roberto Tuchman [a,b,*], Michael Alessandri [c], Michael Cuccaro [d]

1

2

If epileptiform activity is found in a child with ASD without seizures, interpretation of these findings and any intervention or action needs to done within the clinical context of the individual child's symptoms and developmental trajectory. If the EEG shows epileptiform activity that can be correlated directly to either regression of a particular skill especially if the EEG is markedly increased in sleep then the intervention strategies used for epileptic encephalopathies should be considered. Re-assessment of treatment response and monitoring for side effects of the medications used needs to be done on an ongoing regular basis.

The other scenario is the child with ASD and an epileptiform EEG in which the EEG shows only occasional spikes. The paradigm for treatment in this scenario is that of transient cognitive impairment [177]. Treatment for this group is very controversial and requires careful documentation that these spikes are directly linked to the language, cognitive or behavioral dysfunction. If treatment is pursued, careful re-assessment at 3 month intervals with clinical, neuropsychological assessments, and serial EEGs should be carried out.

Take home messages

- **L’associazione DSA-epilessia complica certamente la presa in carico farmacologica del bambino/adolescente (interazioni farmacologiche, effetti avversi “incrociati”, ecc.)**
- **Necessità di “individualizzare” e di monitorare bene nel tempo la terapia**
- **Possibilità, almeno in alcuni casi, di curare epilessia e disturbi comportamentali con lo stesso farmaco**
- **Sostanziale consenso sulla necessità di essere “interventisti” in caso di encefalopatia epilettica (ad es., SLK o ESES), ma non sul trattamento dell’EEG in presenza di regressione autistica senza epilessia**