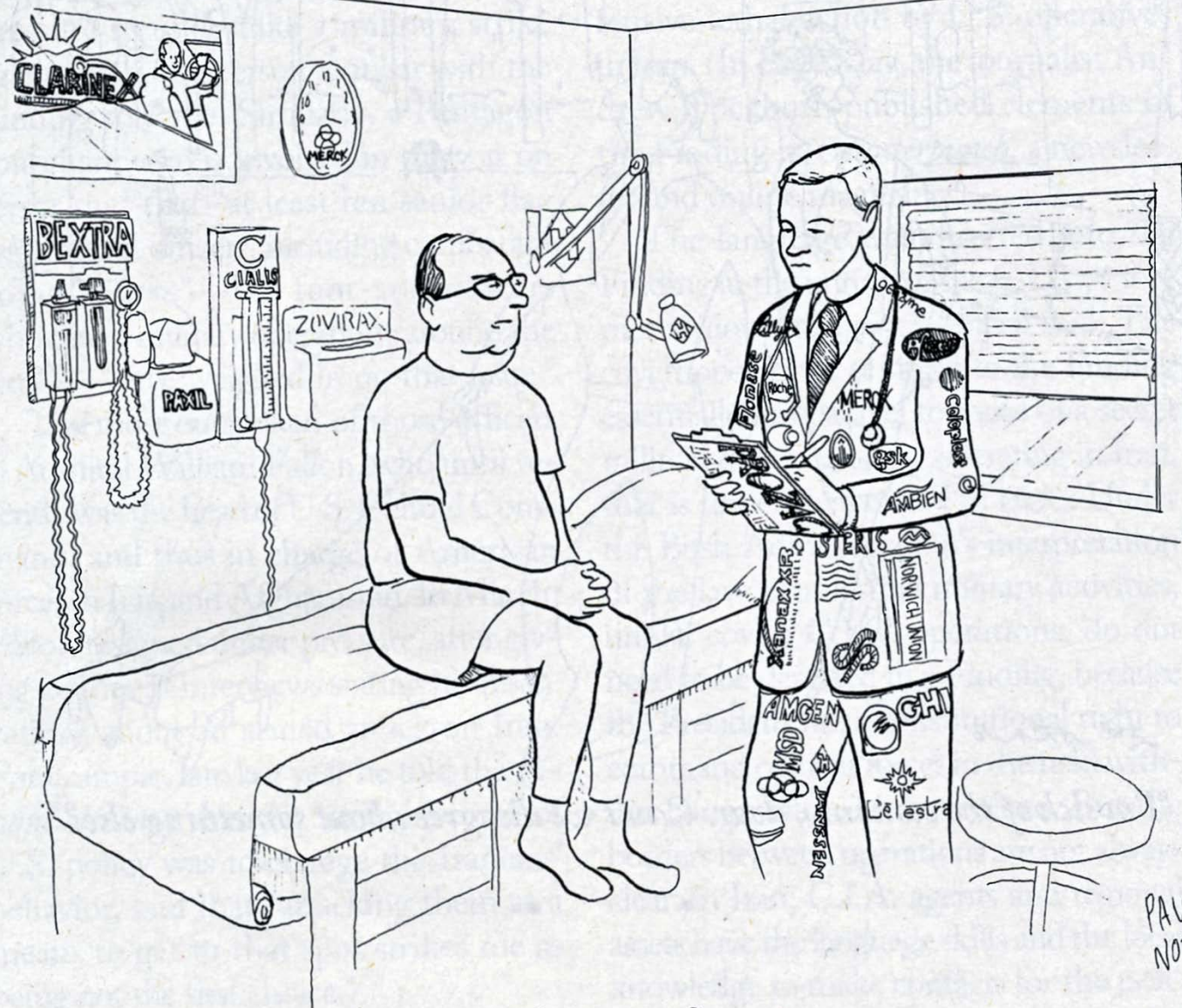


Comorbidities & Pediatric Epilepsy

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Disclosure: W^m Davis Gaillard

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- Earn livelihood (salaried) from caring for children with epilepsy
- Co-Investigator (Not PI & no salary support) on several Pharmaceutical Industry supported AED clinical trials: Rectal Diazepam, Oxcarbazine, Lamotrigine, Zonisimide, Vigabatrin, Tiagabine, Gabapentin, Clobazam, Rufinimide.
- Spouse: Industry trials and consultant
- Stock: General Electric and Siemens
- I do use pens and flashlights from industry with logo.

Learning Objectives

1. Understand the comorbidities of epilepsy
2. Relate the importance of treating comorbidities in children with epilepsy
3. Appreciate the mortality risks of childhood epilepsy
4. Describe the risks of epilepsy and its treatment on reproductive health

Why Epilepsy

- Epilepsy is two unprovoked seizures separated by 24 hours
- 1 in 26 people will meet criteria for epilepsy across life span
- Heterogeneous Disorder (type, etiology, outcome)
- 70% do well; 30% incomplete response to AEDs; 10% do poorly
- Many children will outgrow epilepsy (vs. adults)
- Co-Morbidities may have greater effect than epilepsy on Quality of Life

Comorbidities

- Intellectual Disabilities/Learning disabilities*
 - Social/behavior*
 - ADHD *
 - Anxiety
 - Depression
 - Morbidity & Mortality
-
- *Present at outset of epilepsy
 - Always check family history for LD, ADHD, Mood disorder and anxiety disorders

Cognitive Profiles

- No single profile exists for epilepsy (the epilepsies)
 - Focal epilepsy does not equate to focal deficits
 - Seizures (focal or generalized) may impact a child's functioning across any or all domains of functioning
- Children do not necessarily follow adult profiles
 - Point in development and seizure type determine outcome

Significant Intellectual Impairment

- Up to 1/3 of children with epilepsy have IQ scores below 70 (ID/MR range)
- Risk factors:
 - primary generalized epilepsy, West Syndrome, Lennox-Gastaut Syndrome, partial epilepsy but seizure focus difficult to isolate
 - severe volumetric abnormalities
 - early onset of epilepsy
 - frequent seizures, more episodes of status epilepticus
 - polytherapy
 - comorbid diagnoses (e.g. autism)
- More severe developmental impairment more epilepsy
Berg et al., 2008; Cormack et al., 2007; Hermann & Seidenberg, 2007; Nolan et al., 2003; Vasconcellos et al., 2001

Of remaining 2/3 of seizure disorders...

- Mean IQ in the Low Average range
- Language
 - Recent studies show age appropriate simple, single word knowledge, untimed language skills; but complexity of language impaired

Encephalopathy Broadly Defined

- Three Disease Factors to consider (difficult to untangle)
 - Underlying pathology/cause of epilepsy
 - Epilepsy (severity)
 - Treatment : AED toxicity/ill effects

Attention/Executive Functions

- Attention
 - Commonly observed 30-40%; ?higher with frontal lobe epilepsy or childhood absence epilepsy
 - Need to distinguish inattentiveness of absence seizures from ADHD
 - ADHD Inattentive subtype is more common form
- Executive Function Impairments
 - Less well studied but difficulty with shifting, cognitive flexibility, working memory, organization
 - Parent questionnaire is predictor of performance and helpful in identifying an “at-risk” group of children with new-onset epilepsy

ADHD & Focal Epilepsy

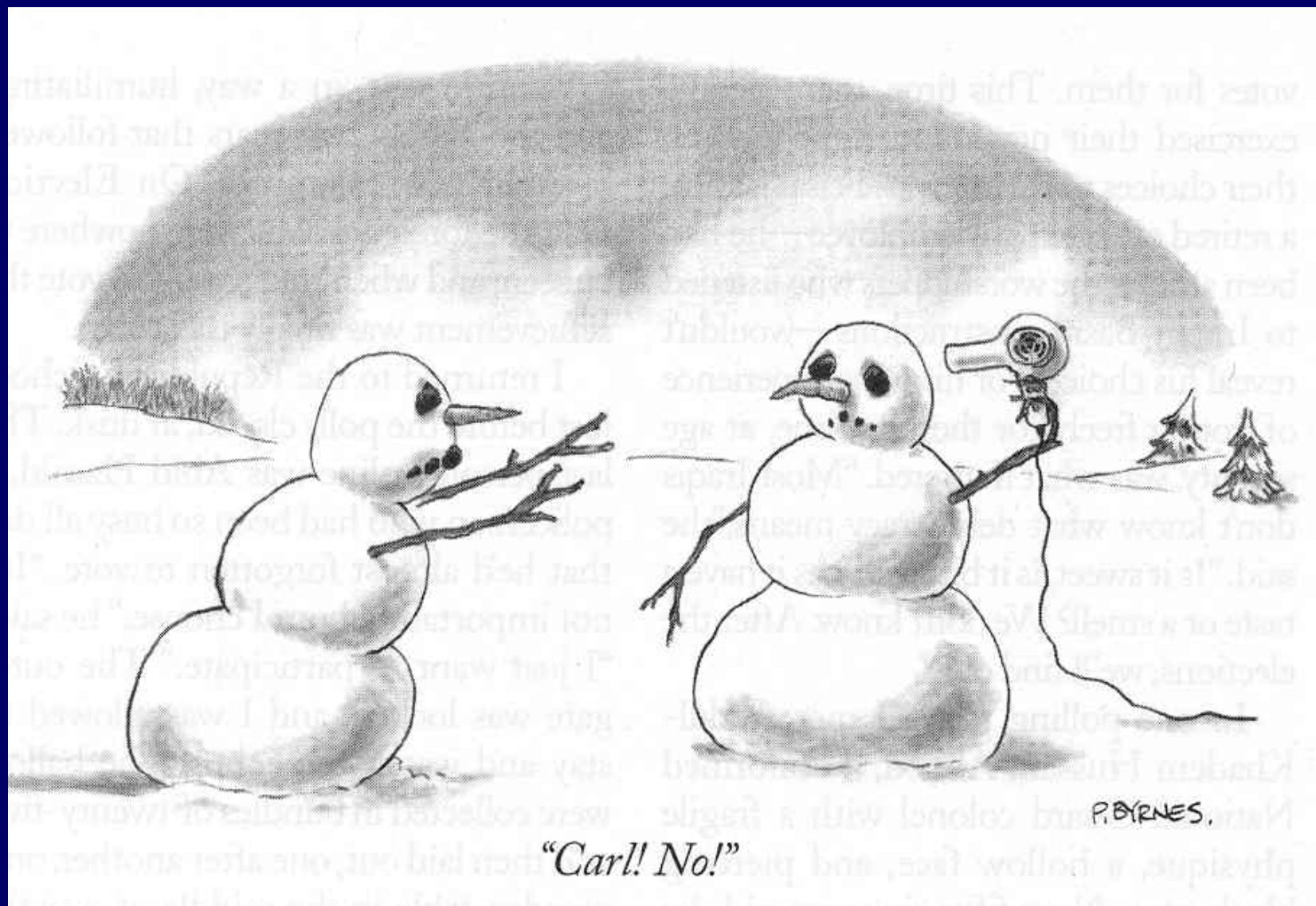
- 75 children localization-related epilepsy (LRE) (mean: 10.09 ± 2.47)
- 75 age-matched controls (mean: 10.13 ± 2.40)
- Direct multimodal, multidimensional measures of attention (Test of Everyday Attention for Children (TEA-ch),
- Parent ratings of attention (DuPaul ADHD rating scales)
- Intelligence testing (Wechsler Abbreviated Scale of Intelligence (WASI-2)).

ADHD & Focal Epilepsy

- LRE group performed worse than the TD group on speeded and complex attention (dual task and dual modality) but did NOT differ on simple visual and simple auditory attention tasks.
- Epilepsy children parents reported clinically elevated symptoms of inattention but not hyperactivity.
- Worse inattention was not associated with IQ, number of antiepileptic drugs, or seizure location.
- Children may not exhibit difficulty until the later years of primary school when demands increase.
- Standard ADHD screening tools may not be a reliable detector of these higher order attention difficulties.
- Monitoring through neuropsychological evaluation is recommended for children with epilepsy.

Memory

- Mixed findings in children but consensus is no lateralizing effect
 - Temporal lobe epilepsy at risk but more consistent if mesial temporal pathology
- Verbal memory at risk regardless of side of focus
- EF issues at play
 - Disorganized free recall but adequate recognition
- Attention problems may explain some global memory problems in childhood; material specificity becomes evident later as attention improves
- Complaints of memory dysfunction – evaluate for depression (.... The most common cause) and medication toxicity



"Carl! No!"

Psychiatric Disorders are Over Represented in Epilepsy

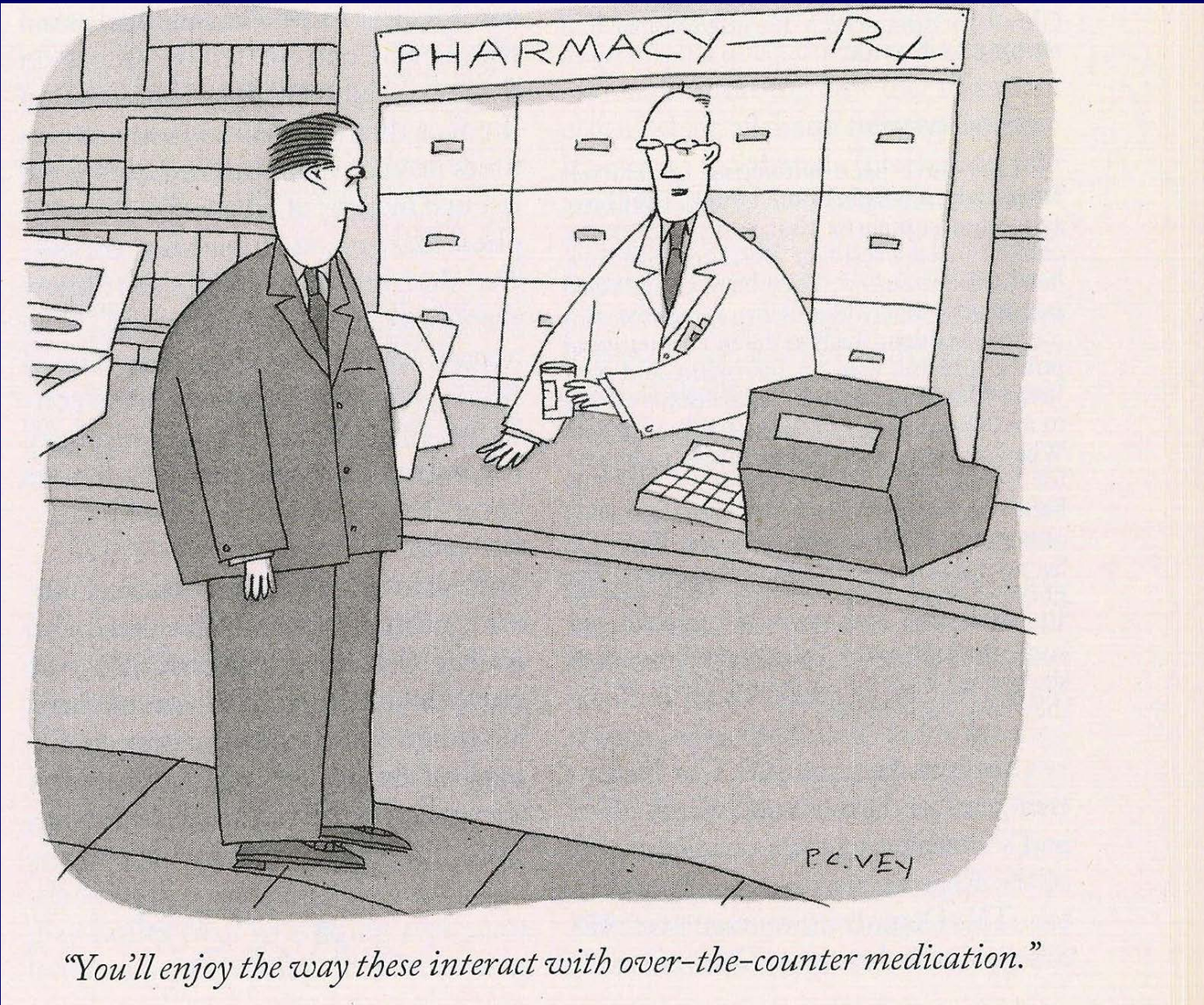
- Isle of Wight Childhood Epidemiology Study:
Psychiatric Illness in 29% epilepsy vs. 16% chronic medical illness
- The rate of psychiatric co-morbidity is nearly 3 fold greater than that found in children with asthma or diabetes.
- Over representation of epilepsy among children and adolescents who attempt suicide
- Suicide rate in adults may be up to 13% compared to 1% in the general population; Temporal Lobe Epilepsy may have 10 times risk.

Psychiatric disorders are the rule for children with medically refractory epilepsy (and those not refractory)

- 33/40 (82.5%) had clinical psychiatric diagnoses:
 - 16/40 (40%) with ADHD or ADHD NOS
 - 13/40 (32%) with Anxiety Disorder
 - 8/40 (20%) with Depressive Disorder
 - 11/40 (28%) with two or more diagnoses
- Temporal lobe epilepsy greater risk for depression
- Anxiety high in parents of children with epilepsy and has secondary effect on child with epilepsy

Treating Comorbidities

- ADHD:
 - Rx with Stimulants; $\alpha 2$ agonists, etc
 - Stimulants in practice DO NOT decrease seizure threshold
- Anxiety:
 - Especially parents
 - Long half life BZP (Clonazepam)
 - SSRIs (Sertraline)
- Depression/Mood disorders:
 - Several AEDs mild antidepressants: CBZ;OXC;LTG;VPA
 - SSRIs mild AEDs will not reduce seizure threshold
 - Fluoxetine and Escitalopram
 - Avoid Wellbutrin (DA antidepressant), which will lower seizure threshold
 - Monitor for “suicidality” with some AEDs*



"You'll enjoy the way these interact with over-the-counter medication."

New Yorker March 13 2006

AEDs:

Almost all AEDs make one drunk at
high dosage & levels

- Phenobarbital
- Zonisimide
- Tiagabine
- Topiramate
- Lacosamide
- Ethosuximide
- Leviteracetam
- Perampanel
- Felbamate
- Carbamazepine
- Oxcarbazine
- Lamotrigene
- Valproate
- Phenytoin
- Gabapentin
- Pregabalin
- Vigabatrin
- Rufinamide

Blue: Rx Mood disorder Orange: Psychosis Green: Dumb

Morbidity & Mortality

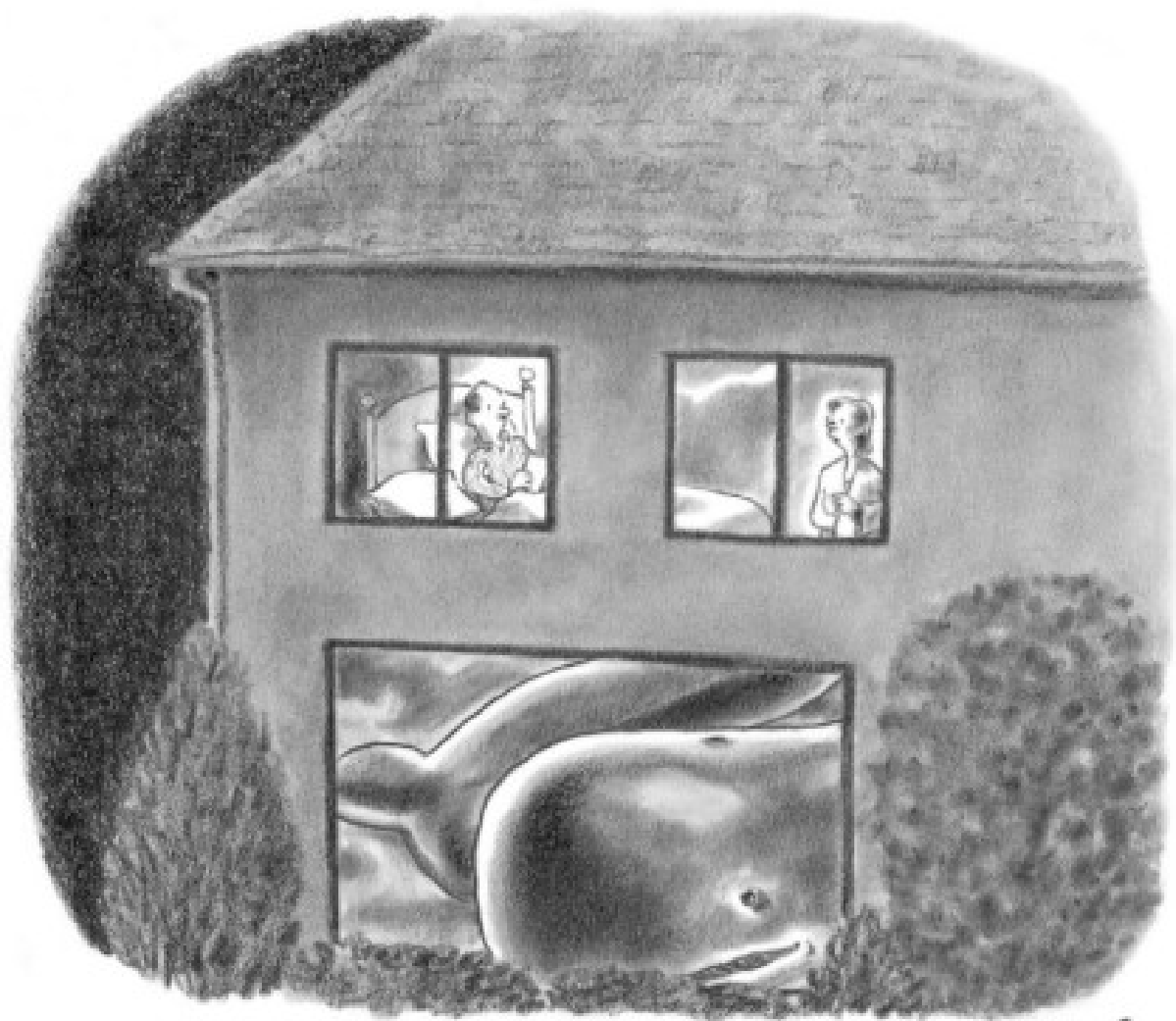
- Accidental injury
 - Trauma/Falls/MVA/Burns
 - Serious accidental injury 17%; Seizure related injury 10%
- Death (standard mortality ratios: children 2; children with epilepsy 6-9)
 - From underlying disease/pneumonia
 - Accidental-Drowning (preventable deaths)
 - During Status epilepticus
 - SUDEP: Sudden unexplained death in epilepsy patients
 - Suicide 5 times population risk
 - Higher in epilepsy, especially TLE

Death & Epilepsy in Children

- Uncomplicated epilepsy 39/100,000 yr
 - Normal exam/ imaging
 - No Intellectual disability
 - No clear cause
- Complicated 857/100,000 yr
 - Abnormal MRI
 - Abnormal Neurological Exam
 - Intellectual Disability
 - Metabolic badness
- All epilepsy 260/100,000 yr

Sudden Unexpected/Unexplained Death in Epilepsy Patients SUDEP

- 2-18% of epilepsy related deaths
- Most common epilepsy related cause of death
- Risk SUD is 24 times general population:
- All childhood epilepsy 33/100,000
 - uncomplicated 9/100,000; complicated 97/100,000.
- 7% all patients by 40 years (24% mort; 3 times normal)
- GTC, frequency, duration, low AED levels, poly therapy, nocturnal seizures BUT in pediatrics subset die early after diagnosis or not “severe” epilepsy. Genetic risk ?
- Unwitnessed seizure, cardiac, respiratory, brain stem, channelopathy
- Risk declines with three or fewer GTC Sz/year in adults

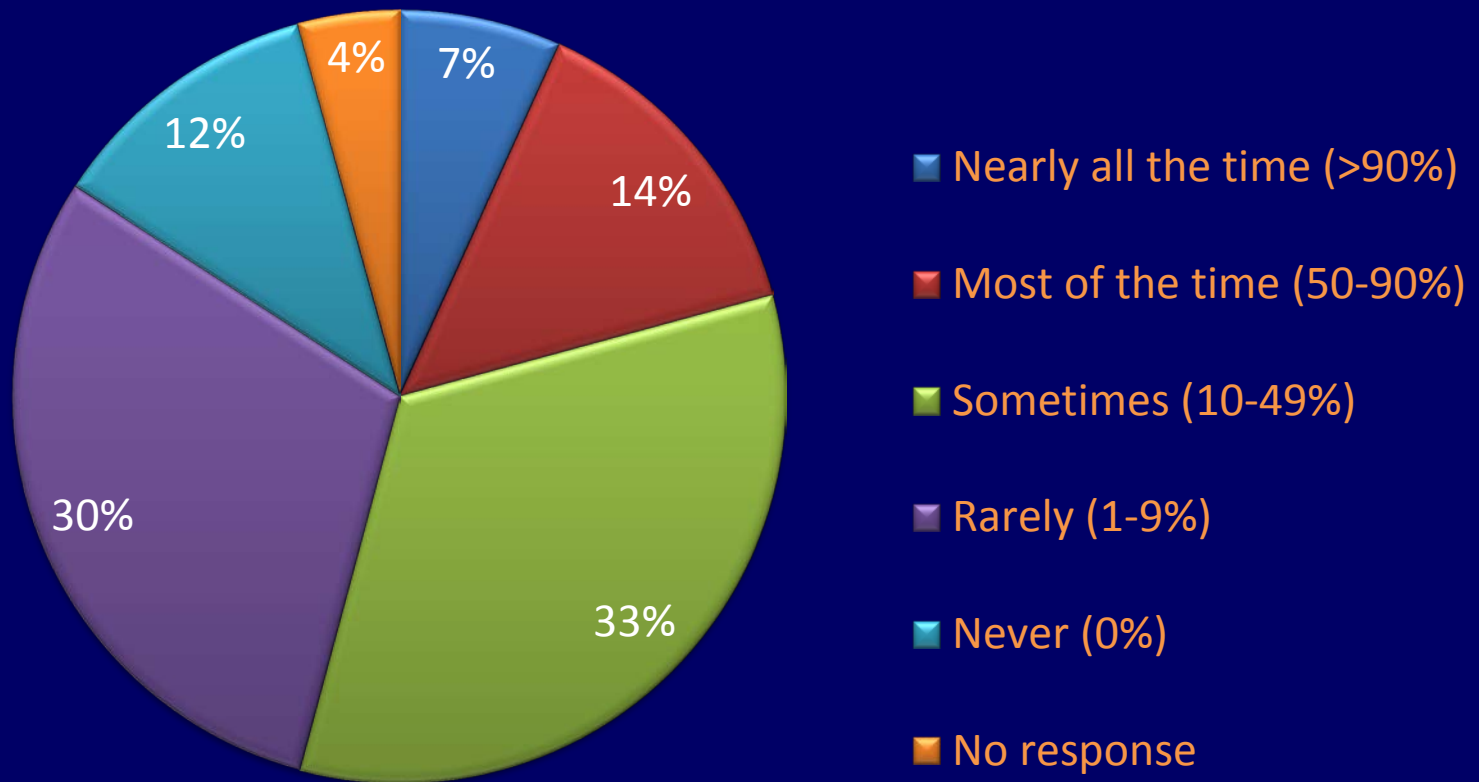


"Either you left the TV on downstairs or we have whales again."

P. DYNES.
CN
COLLECTION

How frequently do you discuss SUDEP with patients or their caregivers?

12% never talk about it; 21% talk about it >50% of the time



Survey Patients & Parents

- 44-62% of adults with epilepsy and 83-94% of caregivers are worried the person with epilepsy may die of epilepsy
- 67% want information at time of first visit
- Does not have immediate or long term negative impact

+SOS-II Epilepsy Risk Discussions

212 Care Giver Responses

	% of CG Responses		
	YES	NO	Not Sure
Rx side effects	85.2	10	4.8
Safety to avoid injuries	75.8	20.9	3.3
Learning/attention problems	66.2	27.6	6.2
Vitamins	54.1	40.1	5.8
Death	40.0	51.0	9.0
SUDEP	14.6	54.9	30.5

How many children & families are informed they have a diagnosis of Epilepsy...

Bone Health

- Enzyme inducers, many AEDs
- Ergo Vitamin D levels low
- Osteoporosis/fractures
- Assess 25-OH Vit D levels
- 20-30 borderline
- <20 abnormal
- Supplement 400 IU day (multi-vitamin); if low add ~1000 IU (adults its up to 5,000 IU) & Ca++ (Tums (equivalent) BID 500-750 BID)

Reproductive Health

- OCP metabolism induced by AEDs; ergo less effective
- Use 2nd method as well (e.g. barrier method)
- Polycystic Ovarian disease with Valproate (VPA)
- Birth defects/Congenital malformations 4%:
seizures, especially GTC are bad, as are many AEDs
- Most AED mono Rx risk is 2-4%; a little higher for PB and DPH, higher risk with higher AED dosing/levels and polytherapy
- Valproate: 6-13% especially spinal dysraphism,
10 pt IQ decline/ ASD

Reproductive Health

- Plan before pregnancy as these are first trimester events. Optimize seizure control, minimize AED number and dosing
- Vitamin K, administer 10 mg/d at 36 wks gestation
- Folate deficiency: all females reproductive age folate 1-5mg supplementation especially if Rx VPA
- Fetal ultra sound
- Be careful about wording of discussion (AEDs are not contraceptives)

The Autisms

- EEG abnormal 30-40% patients
- Epilepsy 10-15%
- No specific kind of epilepsy or focus
- Use standard Rx
- <1% will have Landau-Kleffner or Electrical Status Epilepticus of Sleep (requires sleep during EEG) (Treatable: e.g. Rx Steroids)
- Epilepsy Surgery less likely effective for children with ASD
- TSC % early treatment on developmental outcomes

Quality Of Life

- Freedom from seizures
- Freedom from ill effects of medications
- Capacity to drive (3 mo seizure free MD, self report to DMV)
- Less depression
- More education
- More employment
- More independent living
- Less Injury and death
- Identifying and treating co-morbidities
- Better QOL

Conclusions

- Co-Morbidities common in epilepsy populations
- May be more important clinically than epilepsy
- Can be identified and treated: But must ask
- Most are present at outset, little evidence they deteriorate with time
- Bone & reproductive health (at the proper age) should be discussed, monitored, treated
- Safety, Accidental Injury, and Death (while rare) often not discussed but often are the families' greatest concern





"This is what you get for trying to be a wit."

Sudden Unexplained Death in Epilepsy

Patients SUDEP: Clinical Risks

- Symptomatic Epilepsy
 - GTCs
 - Greater frequency
 - Longer duration (childhood onset)
 - Low AEDs levels
 - (Poly therapy)
 - Nocturnal seizures
 - Lack of remission
-
- BUT in pediatrics subset early after diagnosis or not deemed “severe”

Death in Epilepsy

	All-Cause Mortality (per 100,000 person-years)	SUDEP (per 100,000 person-years)
All US Children	50	NA
All Pediatric Epilepsy	260	33
Uncomplicated pediatric epilepsy	36	9
Complicated pediatric epilepsy	857	97
Long term risks childhood epilepsy	1408	422
All Adult Epilepsy	3-fold higher than age- adjusted general population	100