Drug-Induced Seizure

Pathophysiology and Treatment

Robert S. Hoffman, MD

Disclosure

- I have no relevant financial relationships to disclose.
- There will be no off-label indications of drugs discussed

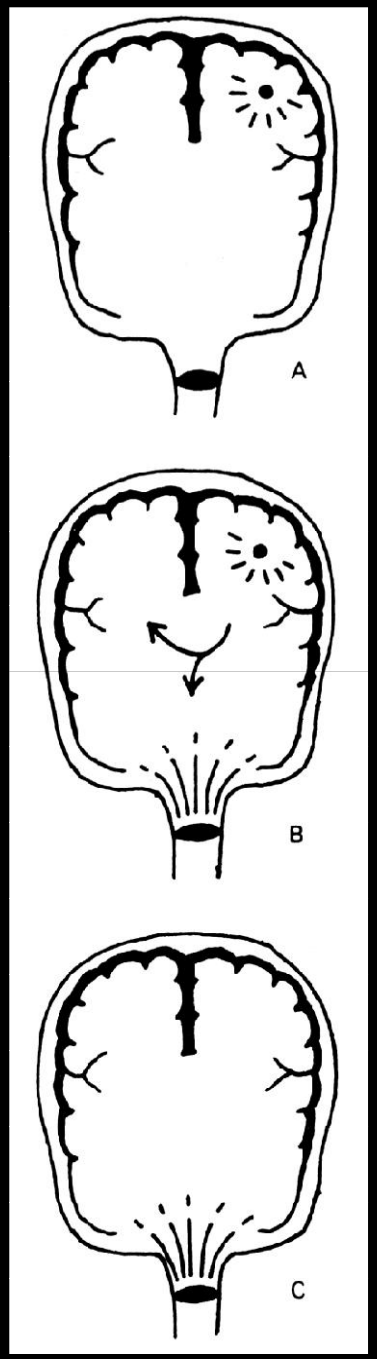
Objectives

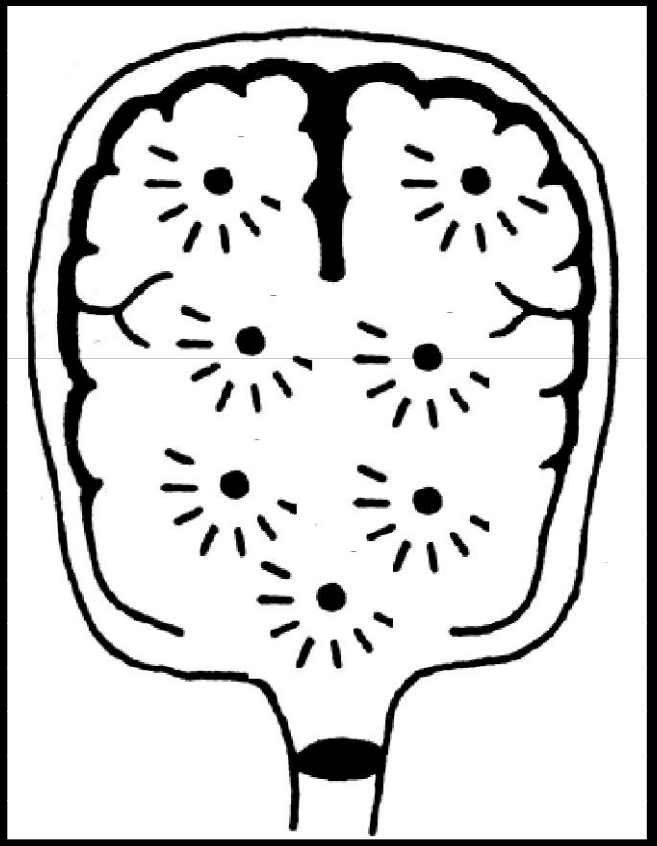
- Highlight mechanisms of drug-induced seizures
- Use a mechanistic approach to develop a rational treatment strategy

Why Do People Seize?

- Impaired inhibition
  - $GABA_A$ antagonism
  - $GABA_B$ agonism
  - Adenosine antagonism
- Enhanced excitation
  - NMDA and other excitatory amino acids
- Disordered conduction
  - Sodium channel blockade
- Metabolic failure
  - Oxygen, glucose, etc

Idiopathic Epilepsy vs Drug Induced Seizures?


A
B
C



REVIEW ARTICLE

CNS Drugs 2000 Aug; 14 (2): 135-146
1172-7047/00/0008-0135/$20.00/0

Drug-Induced Seizures

General Principles in Assessment, Management and Prevention

Kevin Murphy[1] and *Norman Delanty*[2]

Table I. Drugs which have been implicated in inducing seizures[a]

Anaesthetics (general)
Enflurane
Etomidate
Isoflurane
Ketamine
Methohexital
Propofol[b]
Sevoflurane

Antibacterials
Carbapenems (meropenem, imipenem/cilastatin)
Cefalosporins
Erythromycin
Gentamicin
Fluoroquinolones (ciprofloxacin, enoxacin, norfloxacin, ofloxacin)[b]
Nalidixic acid[b]
Penicillins[b]

Antifungals
Amphotericin B
Miconazole

Anthelmintics
Albendazole
Praziquantel
Levamisole

Antipsychotics[b]
Conventional
Chlorpromazine
Fluphenazine
Haloperidol
Pimozide
Thioridazine
Newer
Clozapine
Olanzapine
Risperidone
Sertindole

Hypoglycaemics
Chlorpropamide
Glipizide
Insulin
Metformin
Troglitazone
Tolbutamide

Vaccines[c]
DTP/pertussis
MMR
Rabies

Anaesthetics (local)
Bupivacaine
Cocaine
Lidocaine (lignocaine)
Procaine
Ropivacaine
Tetracaine

Anticholinergics
Atropine
Benzhexol
Benzatropine
Cyclopentolate
Scopolamine

Anticholinesterases
Physostigmine
Donepezil[b]

Antihistamines
Astemizole
Chlorphenamine (chlorpheniramine)
Diphenhydramine
Hydroxyzine
Pheniramine
Terfenadine

Antivirals
Aciclovir (acyclovir)
Amantadine
Ganciclovir
Foscarnet

Immunosuppressives
Azathioprine
Corticosteroids
Cyclosporin[b]
Interferon-α[b]
Tacrolimus/muromomab-CD3 (OKT3)
Sulfasalazine (sulphasalazine)

Miscellaneous
Baclofen
Bromocriptine
Cimetidine
Cycloserine
Dantrolene
Desmopressin[b]
Disulfiram
Epoetin-α (erythropoietin)
Flumazenil[b]
Levodopa
Nicotine
Probenecid

Analgesics
Alfentanil
Morphine
Pentazocine
Pethidine (meperidine)
Dextropropoxyphene (propoxyphene)
Sufentanil
Tramadol[b]

Antidepressants
Tricyclics
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Dothiepin
Doxepin
Imipramine[b]
Nortriptyline
Protriptyline
Trimipramine
SSRIs
Citalopram
Fluoxetine[b]
Fluvoxamine
Paroxetine
Sertraline
Others
Amfebutamone (bupropion)[b]
Guanfacine
Lithium
Maprotiline
Melatonin
Mianserin
Trazodone
Venlafaxine

Cardiovascular agents
Digoxin
Disopyramide
Ergometrine
Ergotamine
Esmolol
Flecainide
Lignocaine
Methyldopa
Methyl-ergometrine
Metoprolol
Mexiletine
Oxytocin
Propranolol
Quinidine[b]
Tocainide

Antiasthmatics
Salbutamol (albuterol)
Terbutaline
Theophylline[b]

Antimalarials
Chloroquine[b]
Mefloquine[b]
Oxamniquine
Pyrimethamine
Quinidine[b]
Quinine[b]

Antineoplastics
Bleomycin
Busulfan (busulphan)
Carmustine
Chlorambucil
Cisplatin
Cytarabine
Methotrexate
Vinblastine
Vincristine

Contrast agents
Diatrizoic acid
Iohexol
Ioparnidol
Metrizamide

Sympathomimetics
Amphetamines
Caffeine
Doxapram
Ephedrine
Methylphenidate
Phenlyephrine
Pseudoephedrine

NSAIDs
Diclofenac
Ibuprofen
Indomethacin
Ketoprofen
Mefenamic acid
Naproxen
Piroxicam
Salicylates

a This table is comprehensive but not all inclusive; the evidence on which a relationship between drug and seizure is based is variable

Table II. Estimation of risk of therapeutic drug-induced seizure

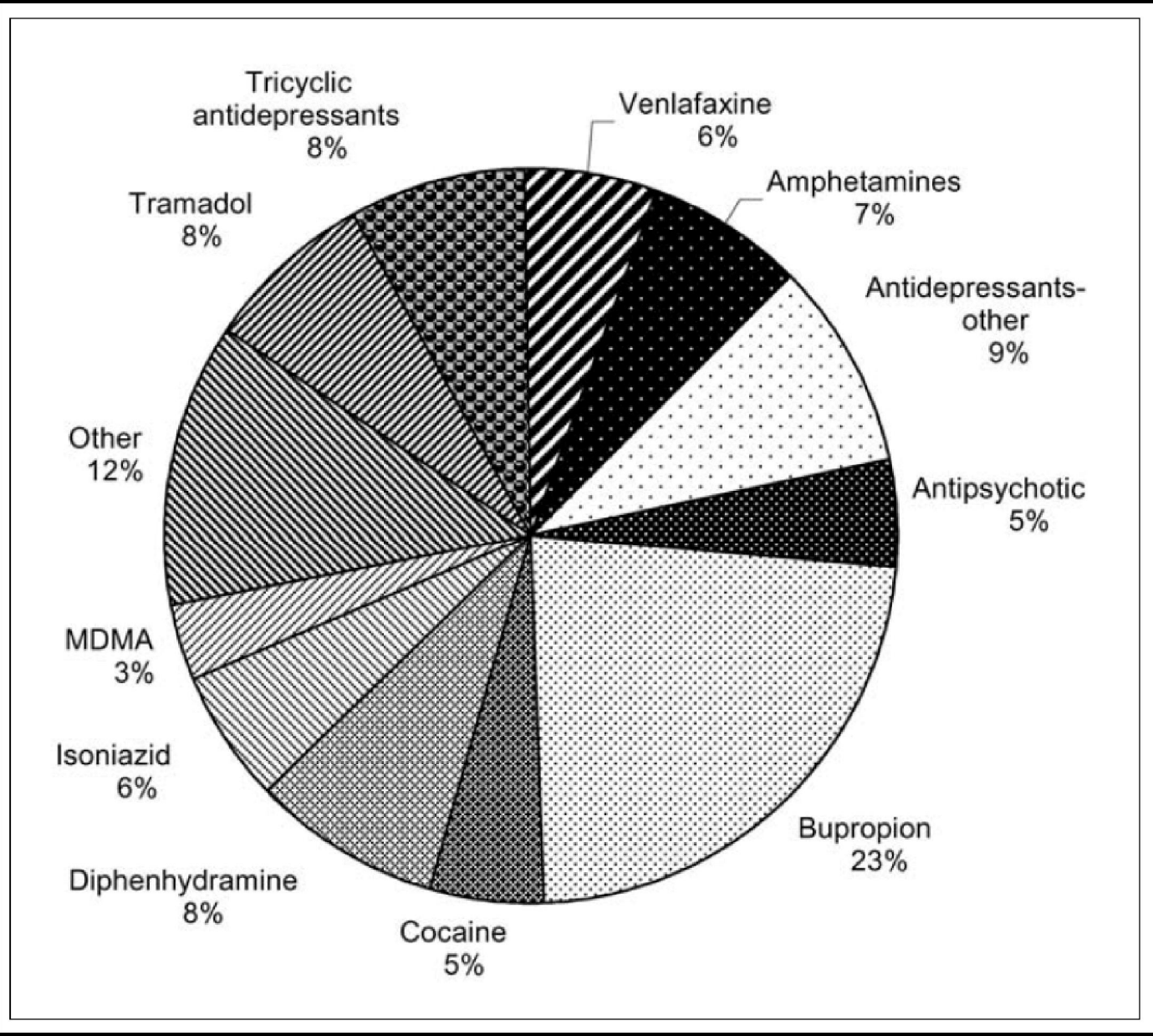
High risk	Medium risk	Low risk
Clozapine	Amfebutamone	General anaesthetics
Contrast agents	(bupropion)	Local anaesthetics
Flumazenil	Antineoplastics	Antidepressants
Penicillin	Fluoroquinolones	Antivirals
Pethidine	Isoniazid	Chloroquine
(meperidine)	Mefloquine	Opioids
Theophylline	Other β-lactam	NSAIDs
	antibacterials	Phenothiazines
	Tramadol	

NSAIDs = nonsteroidal anti-inflammatory drugs.

Evolving Epidemiology of Drug-Induced Seizures Reported to a Poison Control Center System

Josef G. Thundiyil, MD, MPH[a,b], Thomas E. Kearney, PharmD[a], Kent R. Olson, MD[a]

JOURNAL OF MEDICAL TOXICOLOGY ■ VOLUME 3, NUMBER 1 ■ MARCH 2007 15


Tricyclic antidepressants 8%
Venlafaxine 6%
Amphetamines 7%
Tramadol 8%
Antidepressants-other 9%
Other 12%
Antipsychotic 5%
MDMA 3%
Isoniazid 6%
Bupropion 23%
Diphenhydramine 8%
Cocaine 5%

Clinical Toxicology (2014), **52**, 629–634

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2014.918627

informa
healthcare

POISON CENTRE

Seizures after single-agent overdose with pharmaceutical drugs: Analysis of cases reported to a poison center

C. REICHERT,[1] P. REICHERT,[2] F. MONNET-TSCHUDI,[3] H. KUPFERSCHMIDT,[1] A. CESCHI,[1,4] and C. RAUBER-LÜTHY[1]

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[2]*Eawag, Swiss Federal Institute of Aquatic Science and Technology, Dübendorf, Switzerland*
[3]*Department of Physiology and Swiss Centre for Applied Human Toxicology, University of Lausanne, Lausanne, Switzerland*
[4]*Department of Clinical Pharmacology and Toxicology, University Hospital Zürich, Zürich, Switzerland*

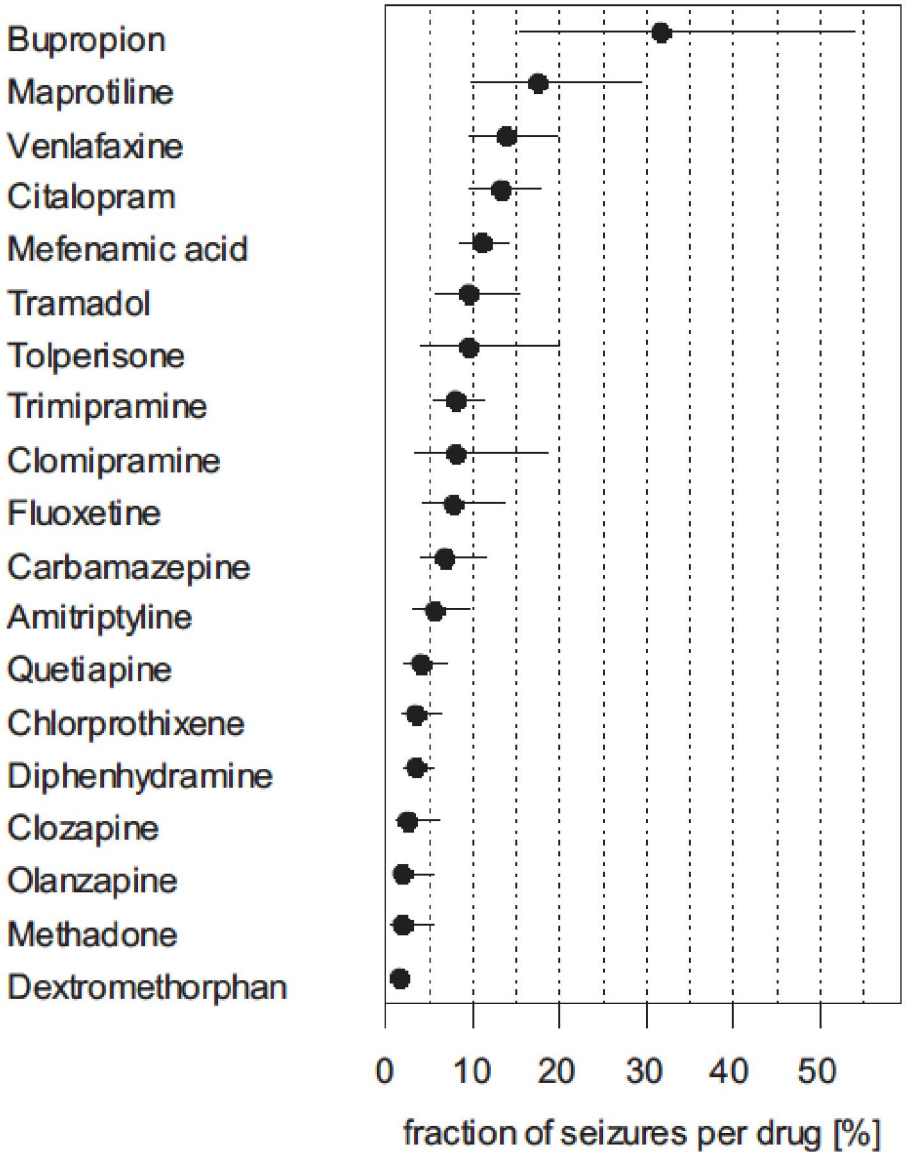
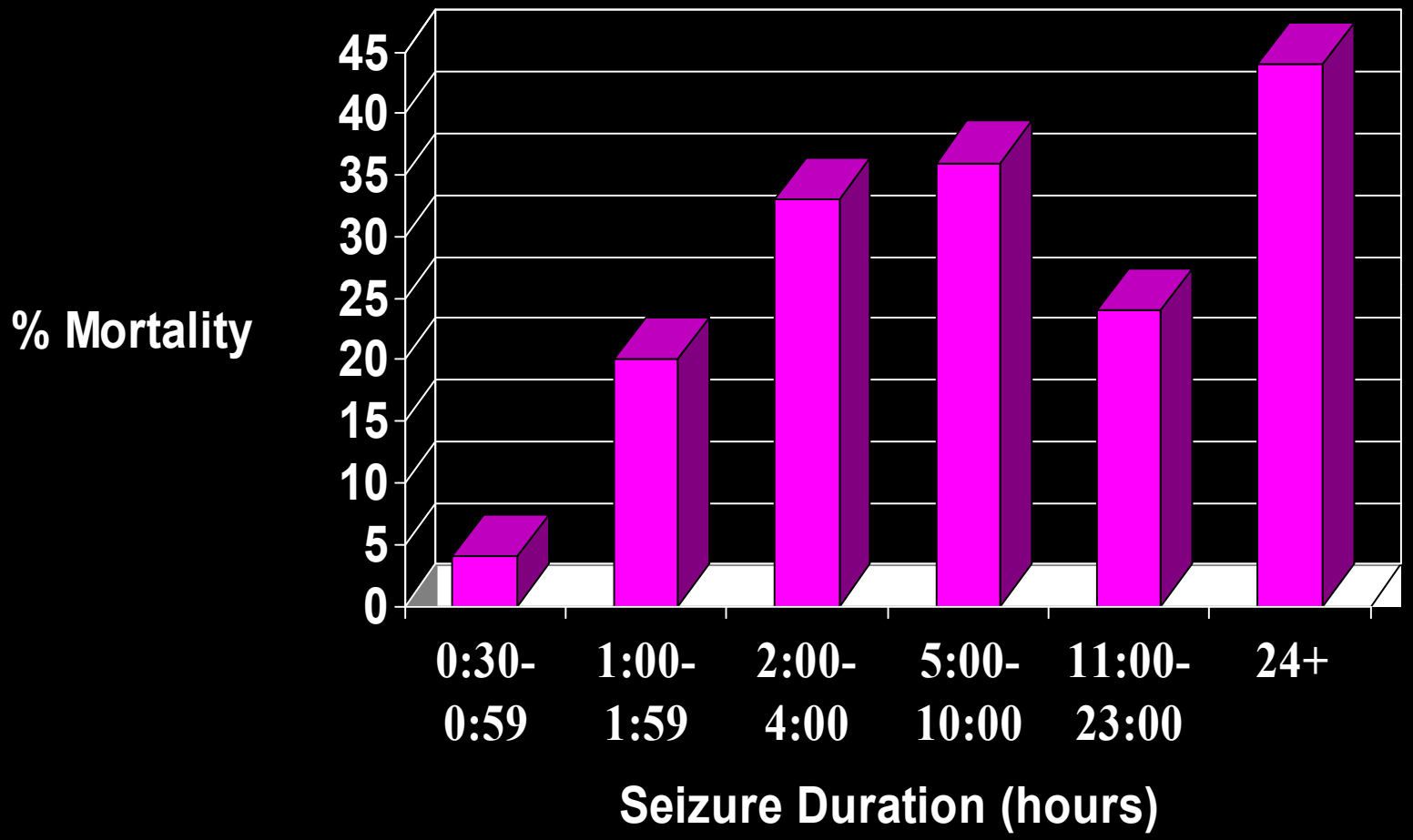


Fig. 2. Seizure potential of pharmaceuticals in overdose. Lines correspond to 95% confidence intervals.

Drug Induced Seizures		Status Epilepticus
Amphetamines	Lidocaine	CO
Anticholinergics	Lithium	Bupropion
Camphor	Hypoglycemics	Hypoglycemics
Carbamazepine	Organophosphates	Isoniazid
CO	Phenytoin	Theophylline
Cocaine	TCAs and others	Tetramine
Cyanide	Theophylline	
Insulin	Tramadol	
Isoniazid	Withdrawal	

Mortality in Status Epilepticus



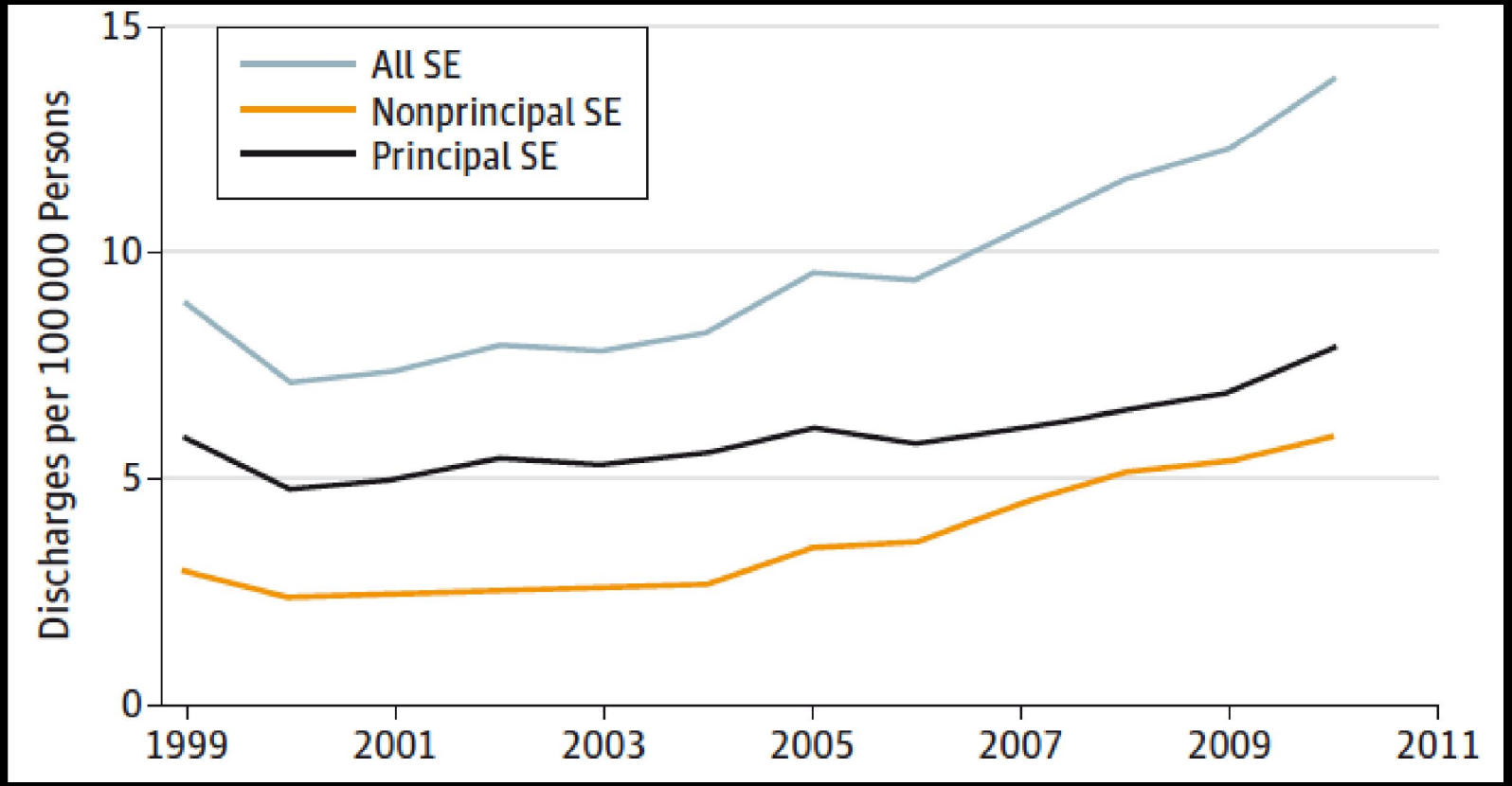
Towne AR, et al. Epilepsia 1994;35:27-34

Original Investigation

Trends in Status Epilepticus—Related Hospitalizations and Mortality Redefined in US Practice Over Time

JAMA Neurol. doi:10.1001/jamaneurol.2015.0188
Published online April 27, 2015.

John P. Betjemann, MD; S. Andrew Josephson, MD; Daniel H. Lowenstein, MD; James F. Burke, MD



First-Line Drugs in Idiopathic Epilepsy

Benzodiazepines
Phenytoin
Barbiturates
Propofol
? Levetiracetam
? Valproate

- **Should drug-induced seizures be treated in the same way?**

Adenosine Antagonism

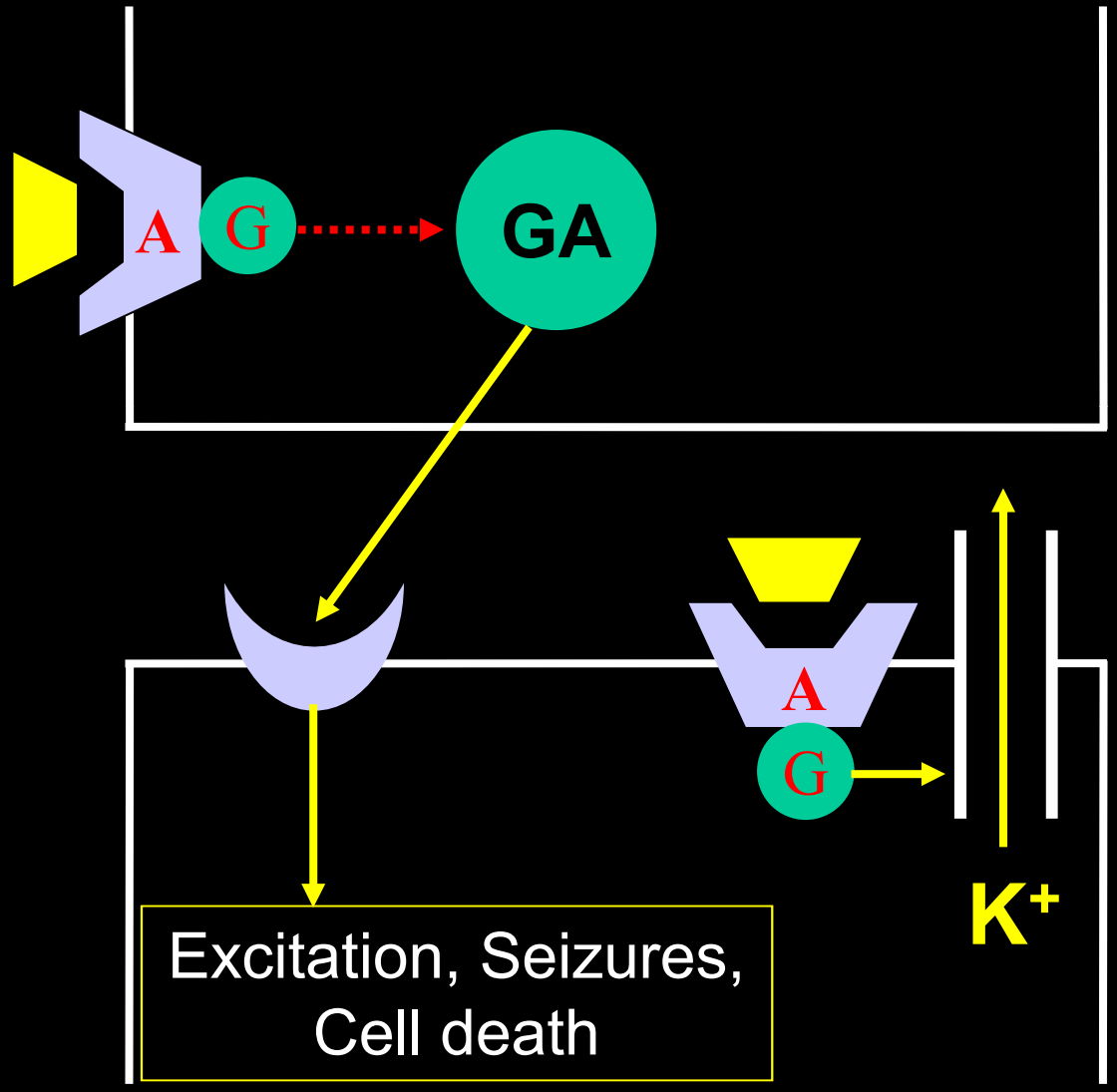
Theophylline / Caffeine

- Complex mechanisms of action
  - Increase in catecholamines
  - Adenosine antagonism
  - Phosphodiesterase inhibition
  - Fluid and electrolyte abnormalities

Caffeine / Theophylline

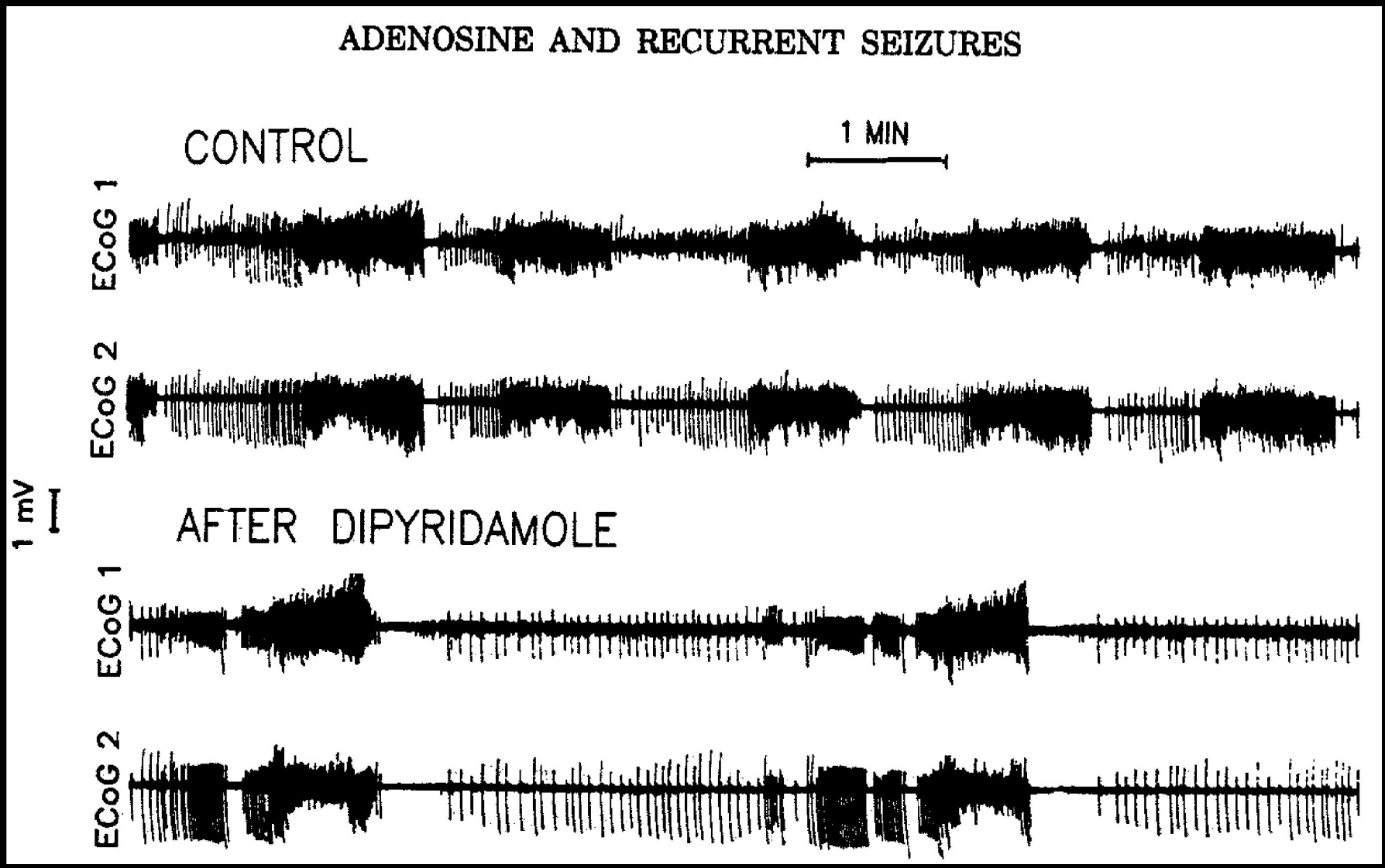
- Toxic syndrome
  - Nausea, vomiting, tachycardia
  - Hypokalemia, hyperglycemia
  - Hypotension (widened pulse pressure)
  - Cardiac dysrhythmias
  - Seizures

Adenosine

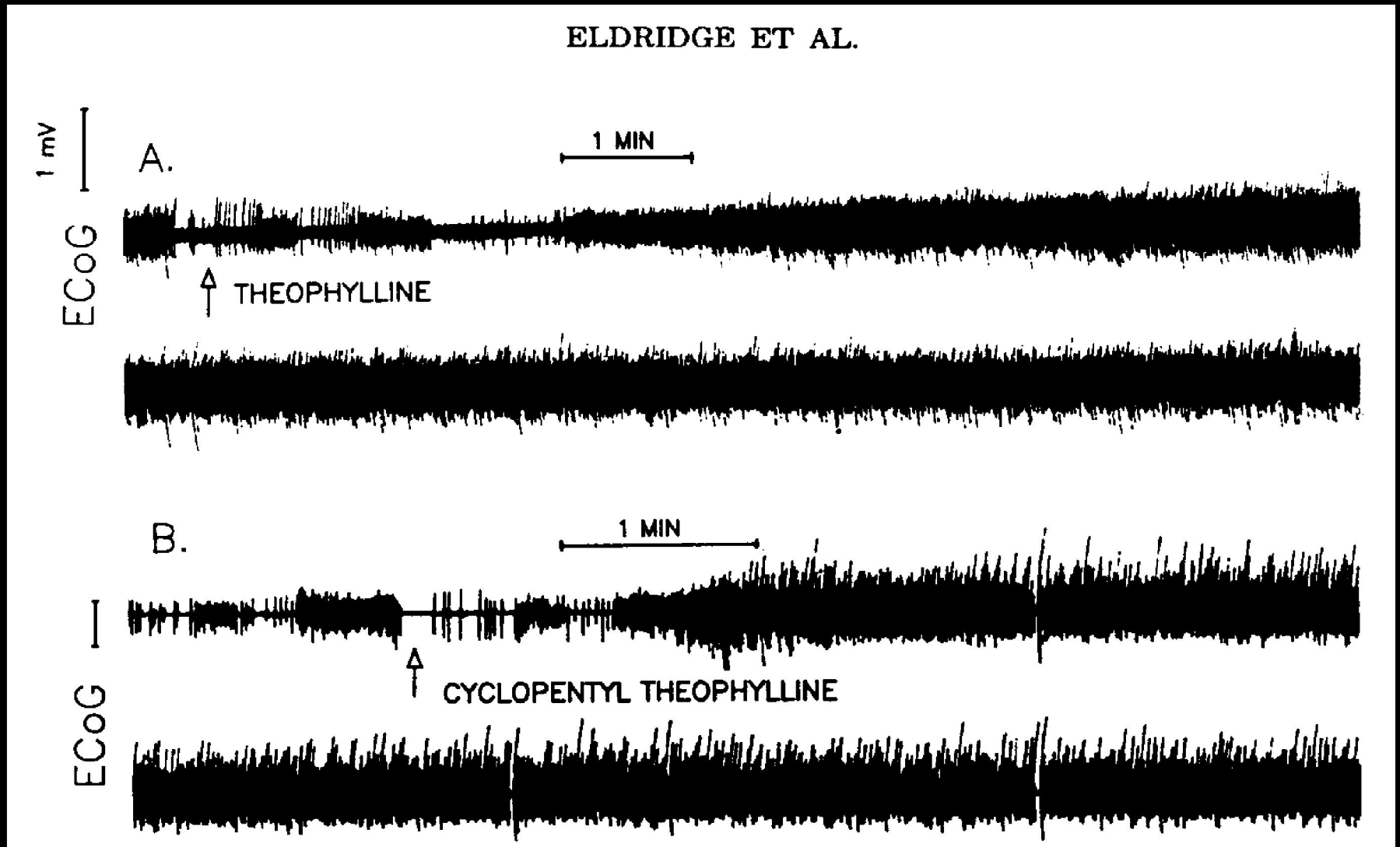


Adenosine

- Net result:
  - Prevents pre-synaptic excitatory neurotransmitter release
  - Reduces post-synaptic effects of excitatory neurotransmitter
  - Supplies critical cells with glucose, oxygen
  - Vasodilation
    - Removes toxic metabolic byproducts



Exp Neurol. 1989 Feb;103(2):179-85.



Exp Neurol. 1989 Feb;103(2):179-85.

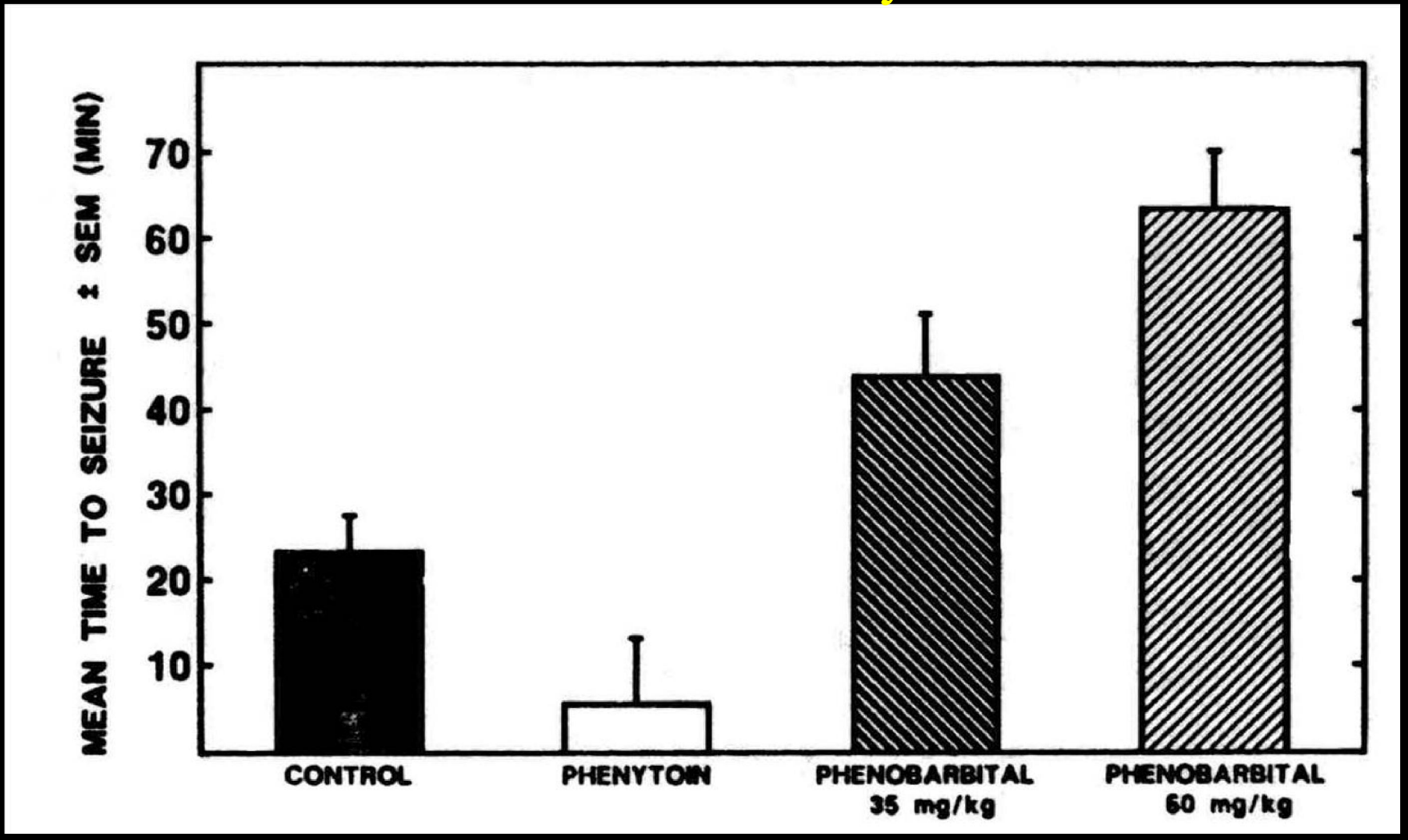
Methylxanthine Induced Seizures

- Implications
  - Poor associated prognosis
  - Adenosine antagonism allows for:
    - Progression to status epilepticus
    - Rapid metabolic failure
    - Subsequent neurological injury

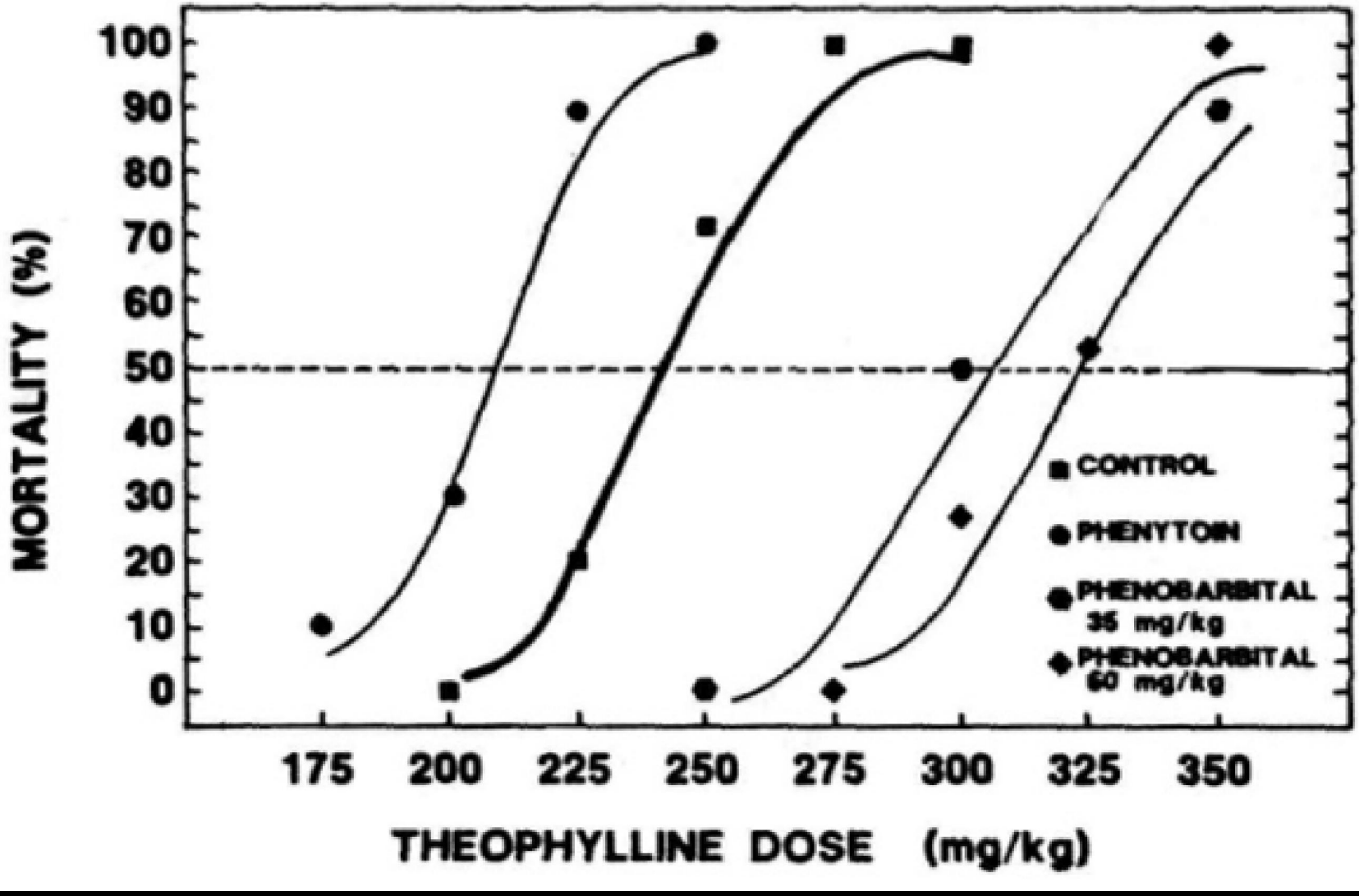
Methylxanthine Induced Seizures

- Treatment
  - A, B, C and D (check glucose)
  - Aggressive seizure control
    - Midazolam, diazepam or lorazepam
  - Next choices?
    - Barbiturate
      - Ultra-short acting over phenobarbital
    - Etomidate?, Propofol?
    - **Avoid phenytoin**

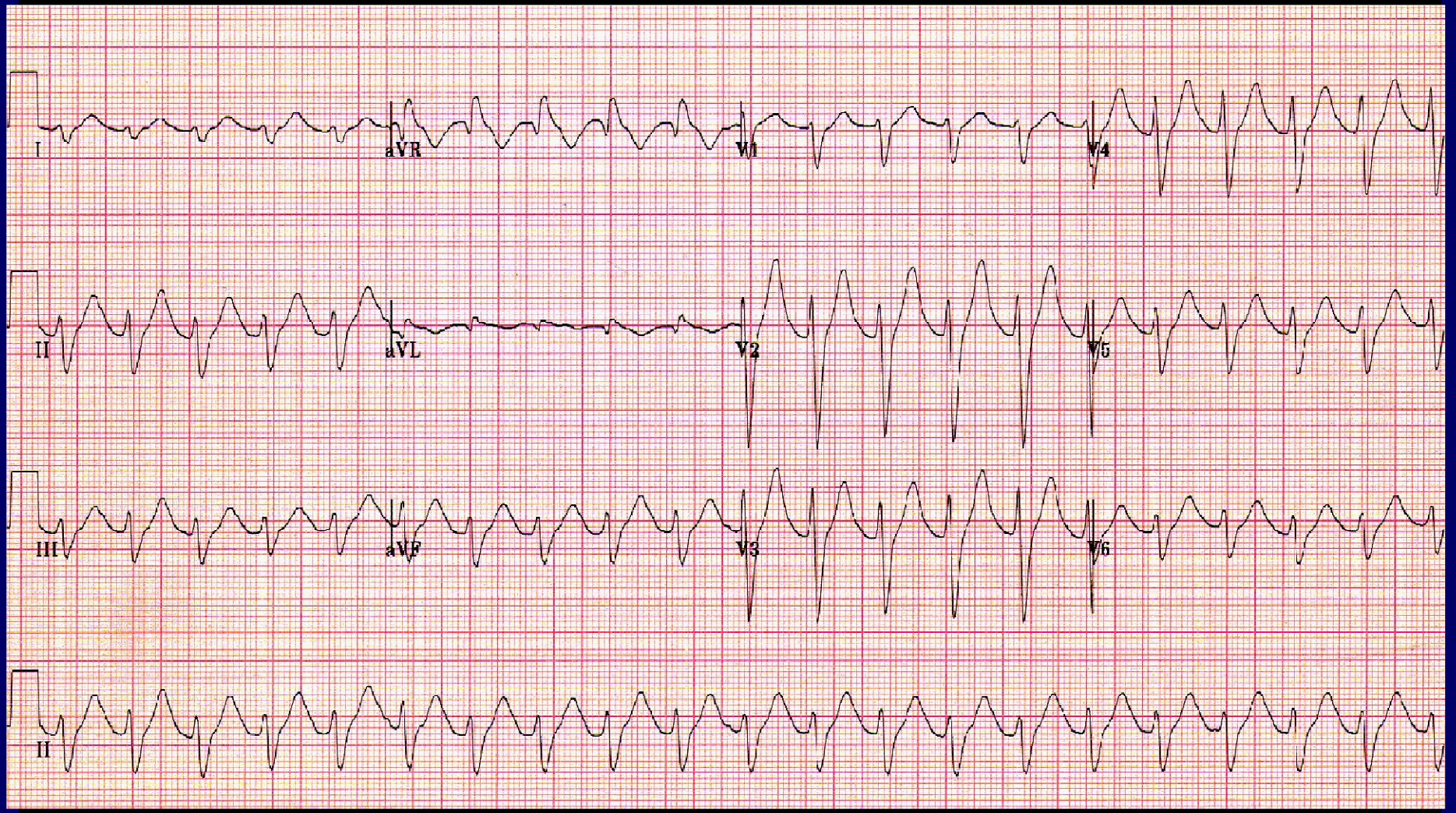
Blake and Massey



Ann Emerg Med. 1988 Oct;17(10):1024-8


MORTALITY (%)
100
90
80
70
60
50
40
30
20
10
0
175
200
225
250
275
300
325
350
THEOPHYLLINE DOSE (mg/kg)
CONTROL
PHENYTOIN
PHENOBARBITAL 35 mg/kg
PHENOBARBITAL 60 mg/kg

Sodium Channel Blockade

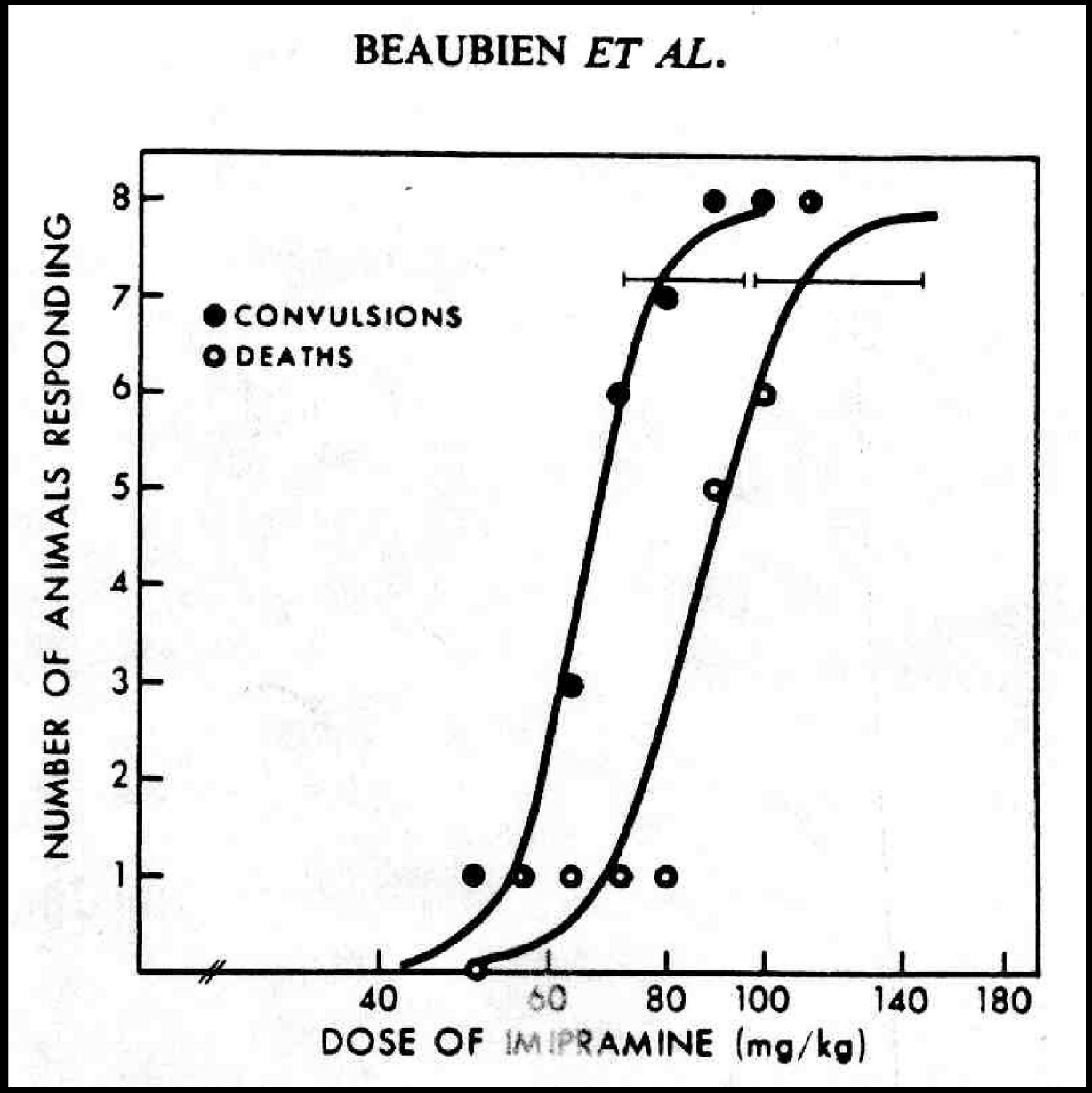

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Tricyclics

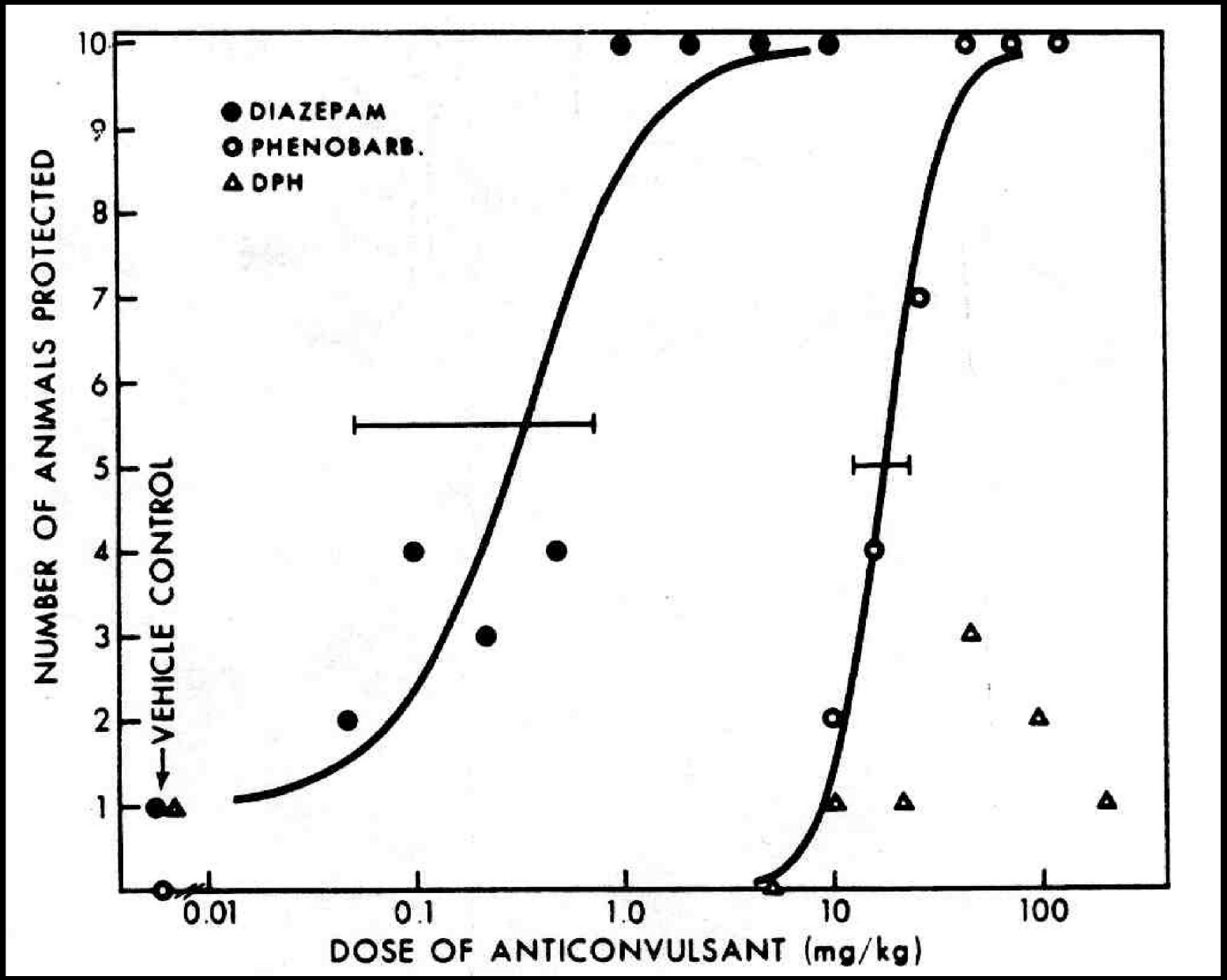
- Complex drugs
  - Block the re-uptake of biogenic amines
  - Block alpha adrenergic receptors
  - Block muscarinic receptors
  - Block fast sodium channels
  - Bind to the picrotoxin receptor
    - GABA antagonism

Phenytoin and TCAs

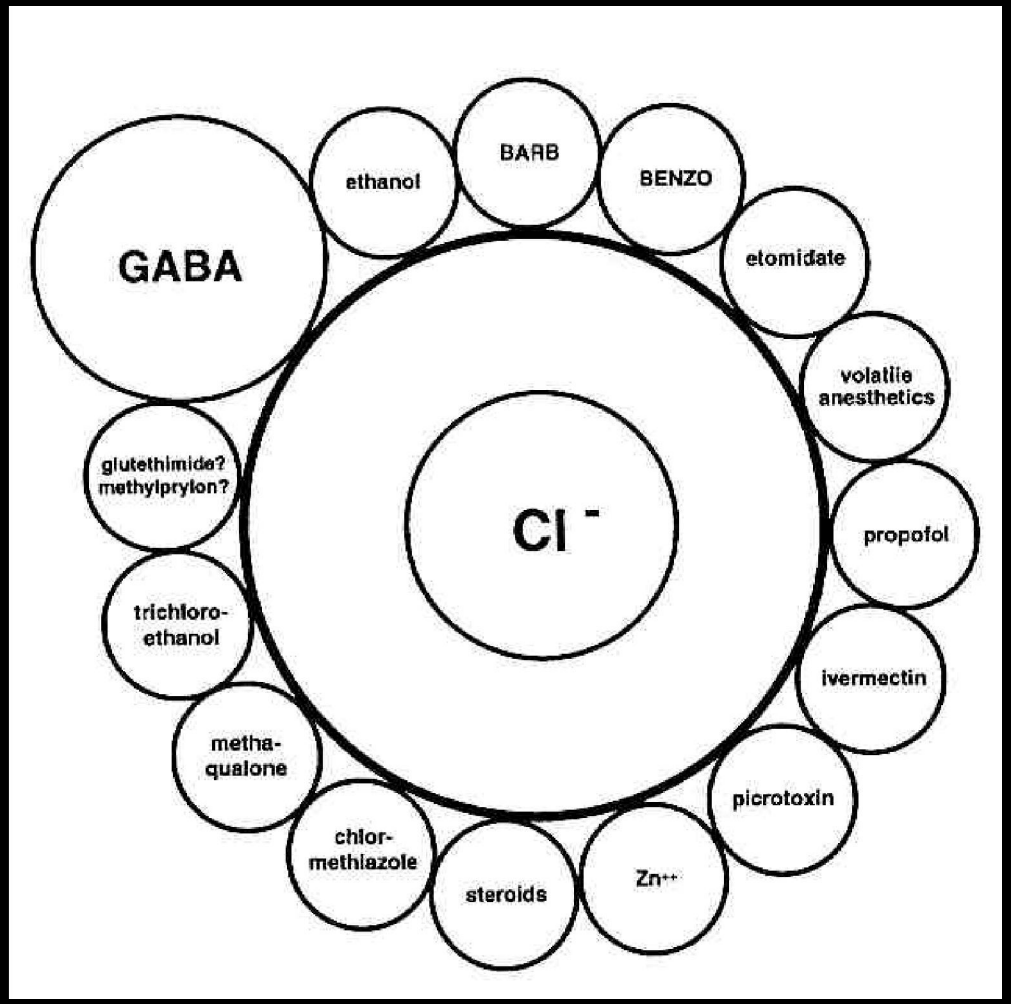
- Once thought to be the drug of choice
  - In theory
    - Narrows QRS
    - Narrows QT
    - Terminates seizures
  - In reality
    - Exacerbates V-tach (Callaham)
    - Doesn't treat seizures

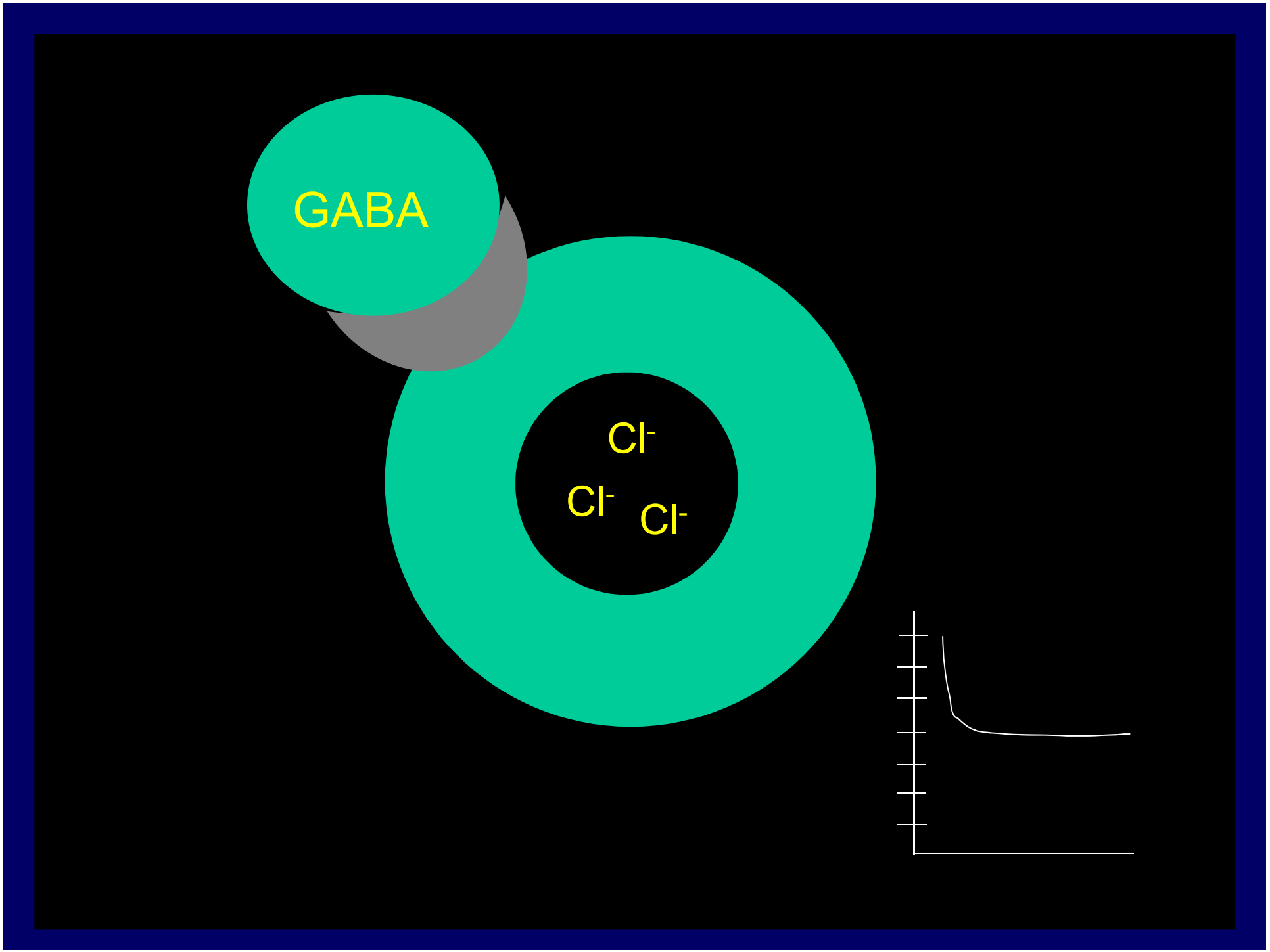


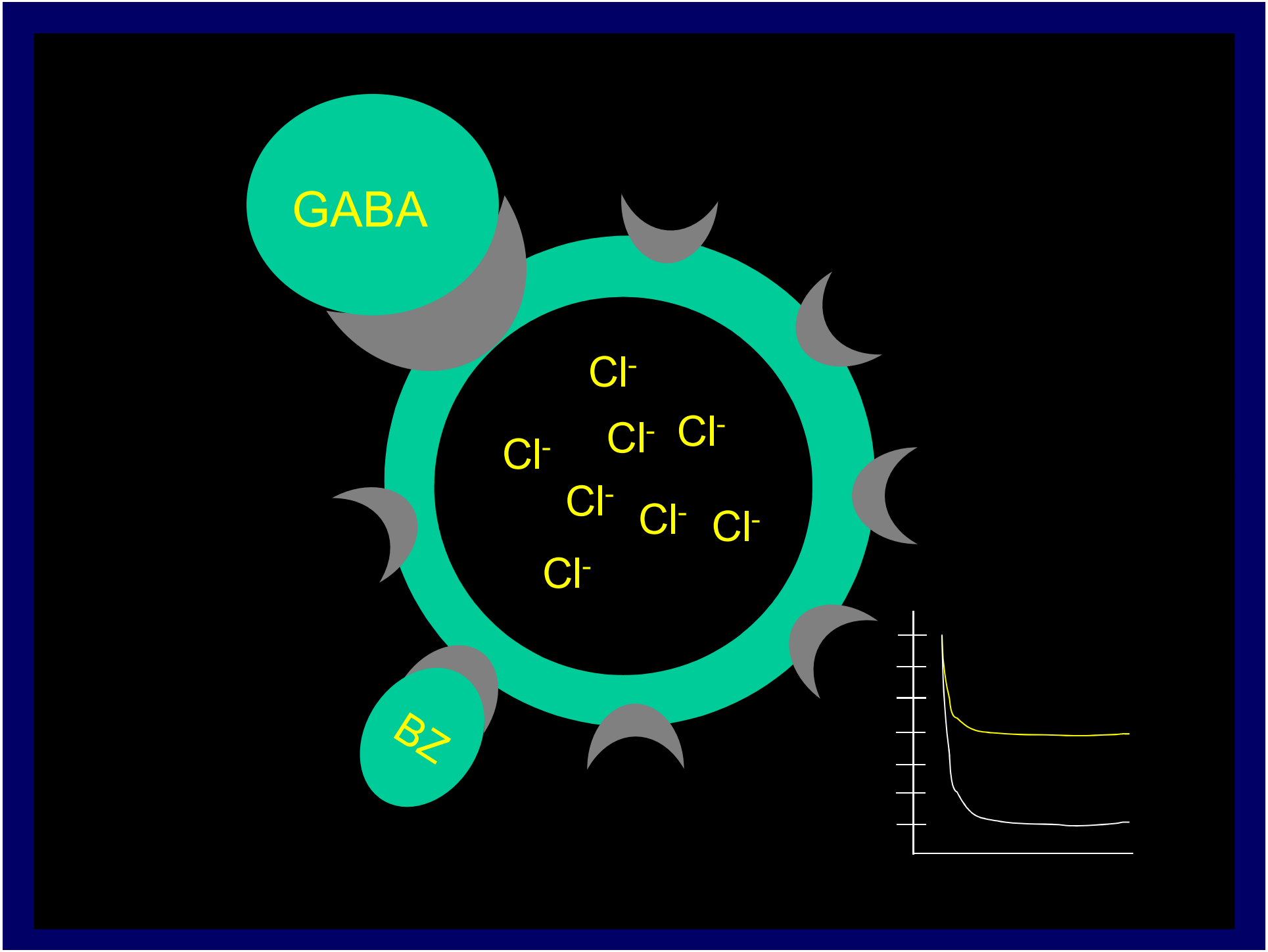
Toxicol Appl Pharmacol. 1976 Oct;38(1):1-6


DIAZEPAM
PHENOBARB.
DPH
NUMBER OF ANIMALS PROTECTED
VEHICLE CONTROL
10
9
8
7
6
5
4
3
2
1
0.01
0.1
1.0
10
100
DOSE OF ANTICONVULSANT (mg/kg)

$GABA_A$ Antagonism



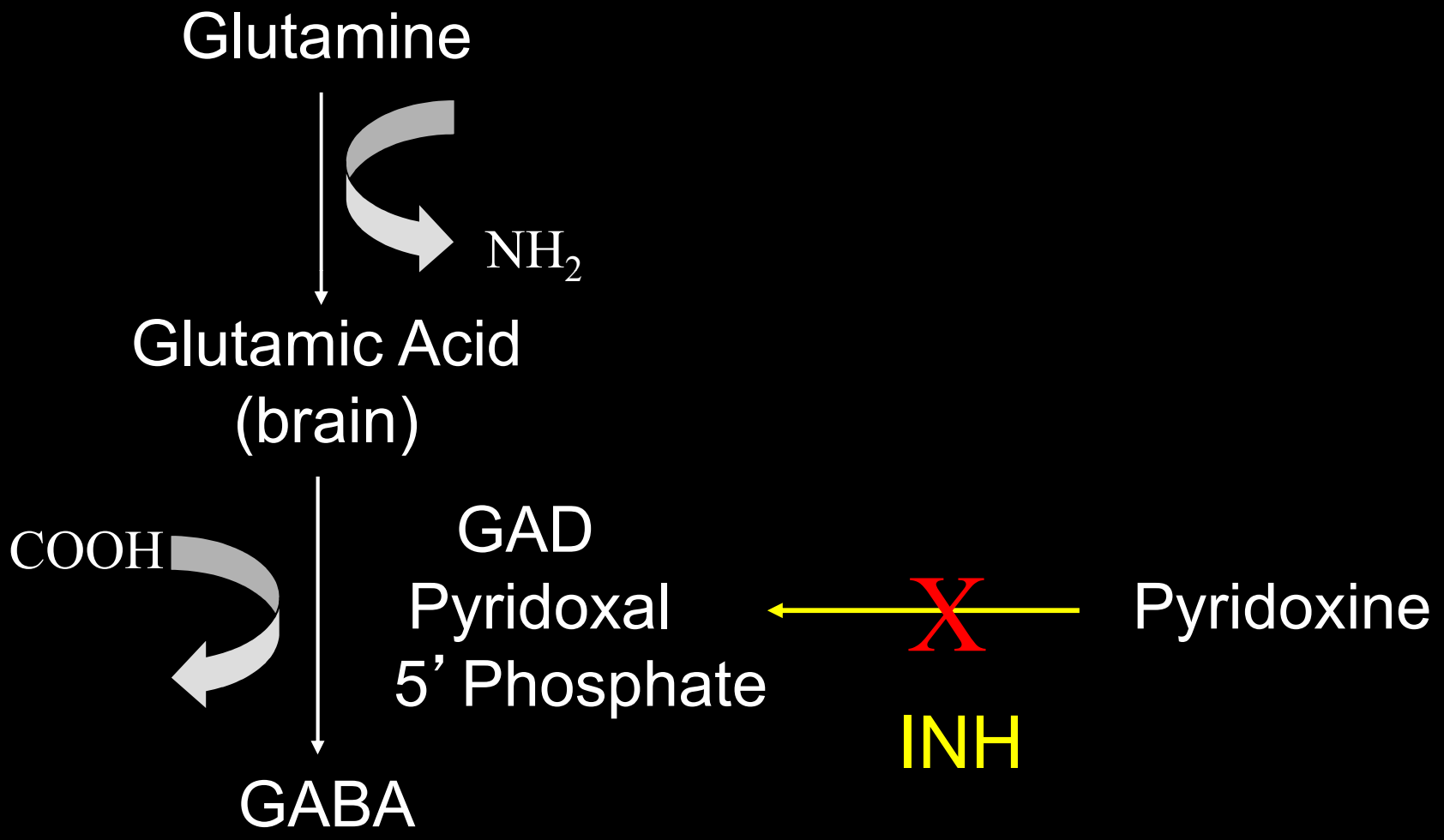

GABA
Cl-
Cl-
Cl-


GABA
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
BZ

$GABA_A$ Antagonism

- Prevent GABA binding
  - Picrotoxin
  - Penicillin
- Altered sensitivity
  - Alcohol withdrawal
- Reduced GABA
  - Isoniazid
  - Monomethylhydrazine

Pyridoxine (B_6) and GABA



Isoniazid

- Most GABA agonists require GABA
  - Try a benzodiazepine
  - No role for phenytoin (doesn't work; Saad)
  - No role for phenobarbital (takes too long)
  - Give pyridoxine (70 mg/kg up to 5g)
    - Chin L: Toxicol Appl Pharmacol 1978;45:713-22

INH Induced Status Epilepticus

- Use intubating barbiturates
  - Open Cl^- channel without GABA
- Consider NMBs to prevent hyperthermia and metabolic complications
- EEG monitoring
- Consider hemodialysis
- Give pyridoxine for prolonged coma
  - Brent: Arch Intern Med 1990;150:1751-3

'Rocket fuel' toxin from poison mushrooms sickens 10 in Michigan

The tell-tale signs of false morel, Verpa bohemica, above, are the attachment of the cap to the stalk at the top of the cap, and the cottony material in the stem. True morels are hollow, said Chris Wright, Midwest America Mycological Information.
(Courtesy MAMI)

Rum Fits

Abstinence and Alcoholic Epilepsy

- Reviewed 241 patients with:
  - alcohol-related seizures as the cause for presentation
  - other symptoms of alcoholism complicated by seizures
- Characterized relationship between seizures and alcoholism

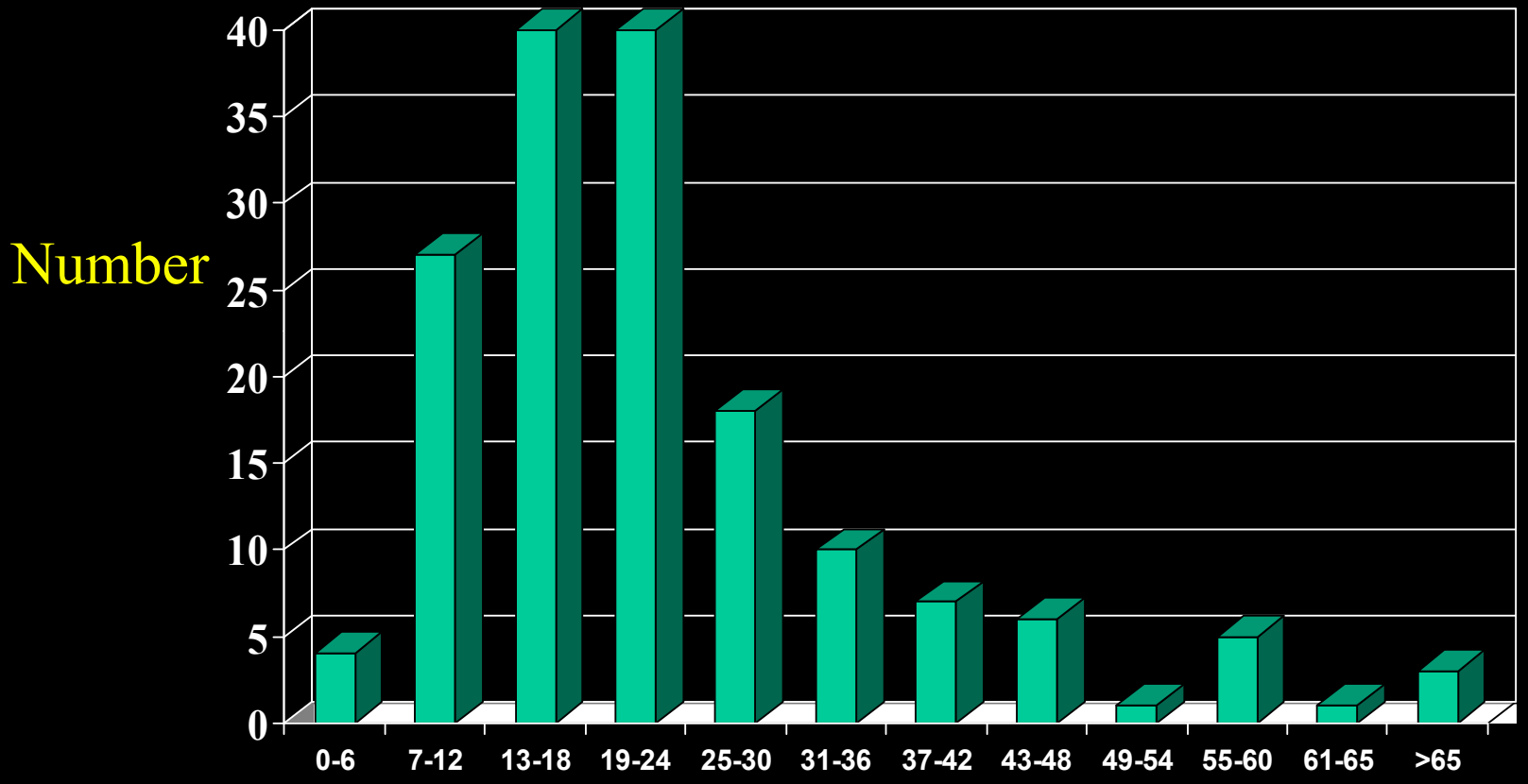
Victor and Brausch: Epilepsia 1967;8:1-20

Age of Onset of Seizures

Age	Number	Percent
>60	13	5.4
30-60	214	88.8
25-30	6	2.5
Under 25	8	3.3

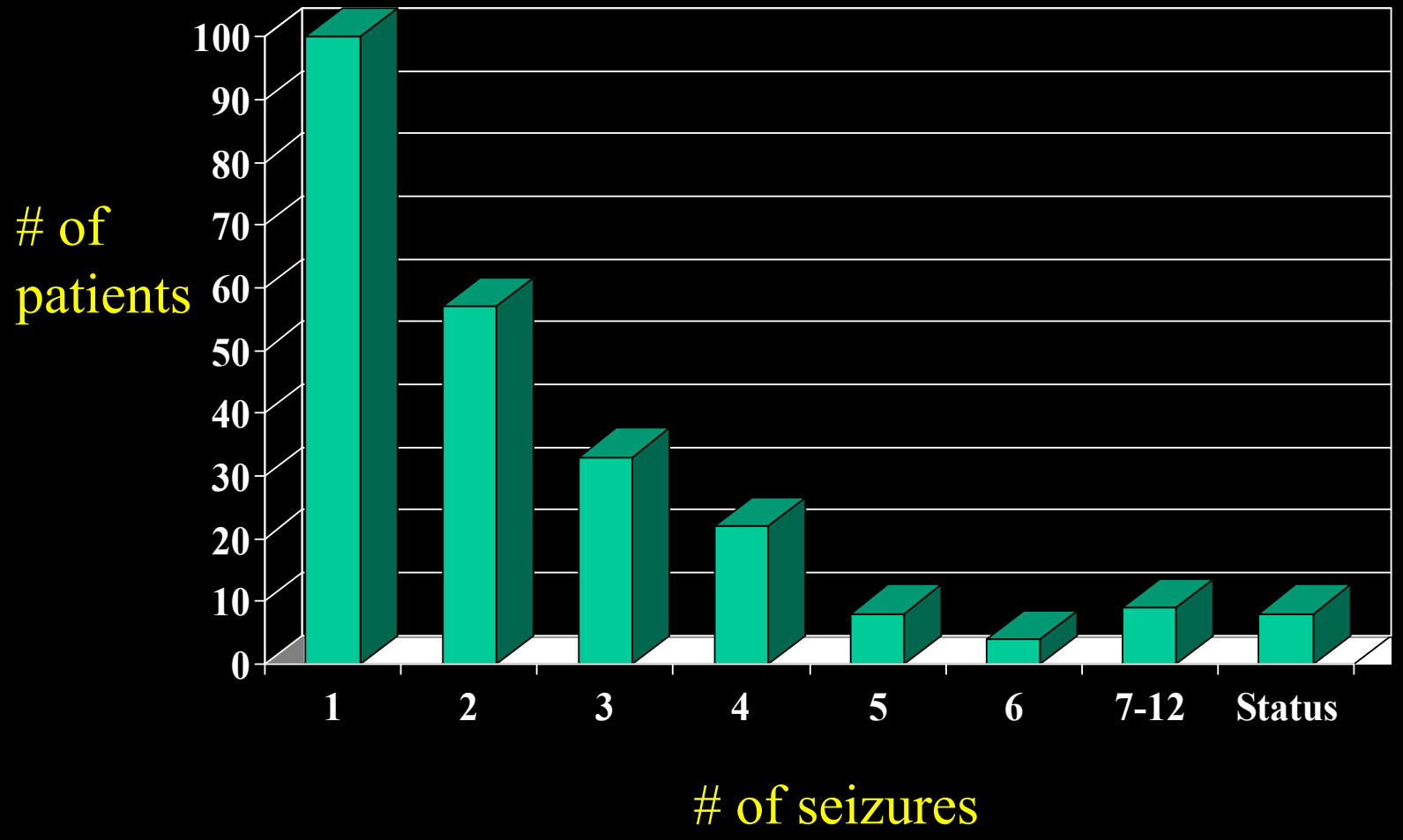
Victor and Brausch: Epilepsia 1967;8:1-20

Onset of Seizures

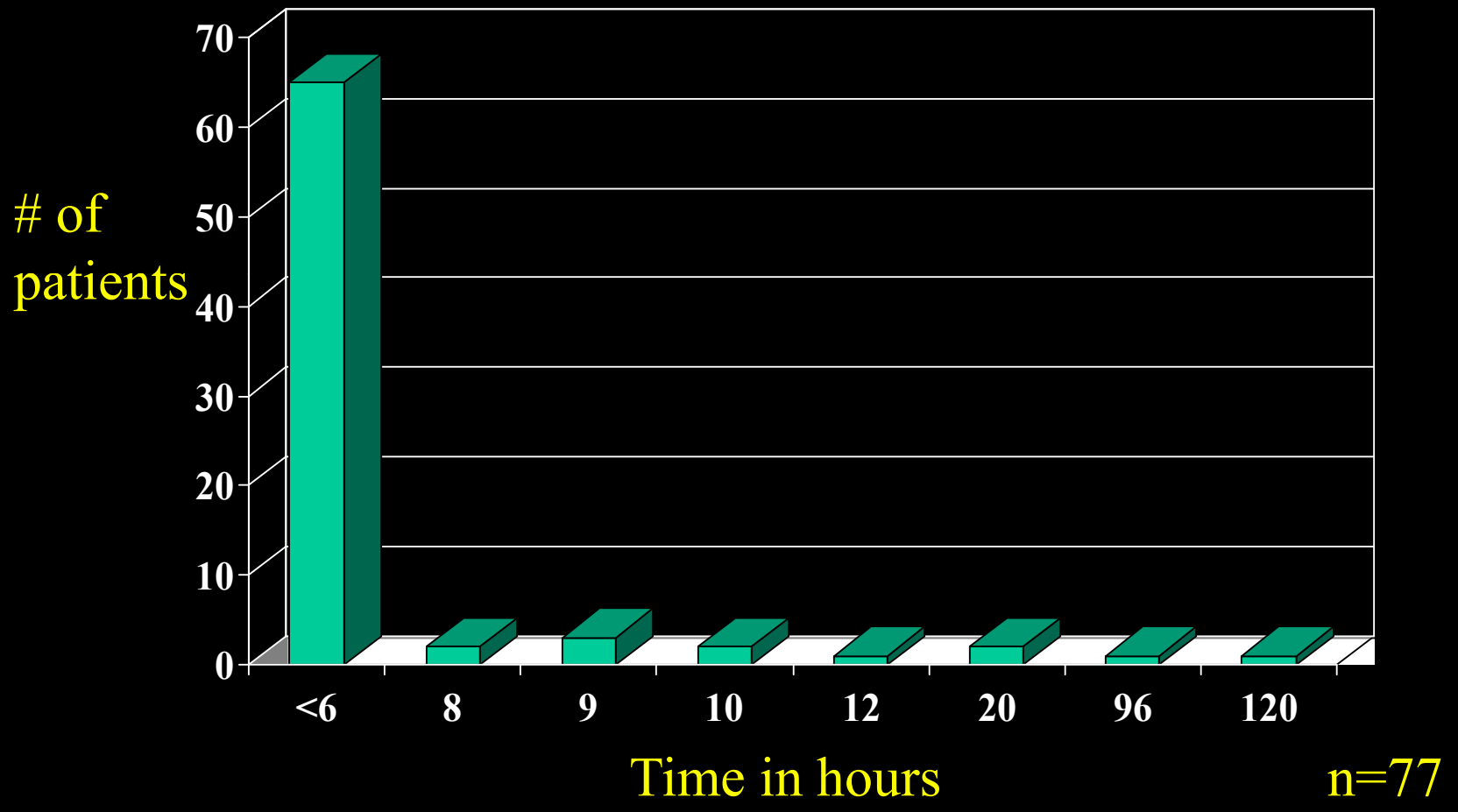


Victor: Epilepsia 1967

Number of Seizures



Time From First to Last Seizure



Ethanol and GABA

- Rats exposed to ethanol for 14 days.
- $^{36}Cl^-$ uptake measured in response to muscimol is decreased by 26%
- $^{36}Cl^-$ uptake measured in response to ethanol is unchanged
- Suggests subsensitivity to GABA

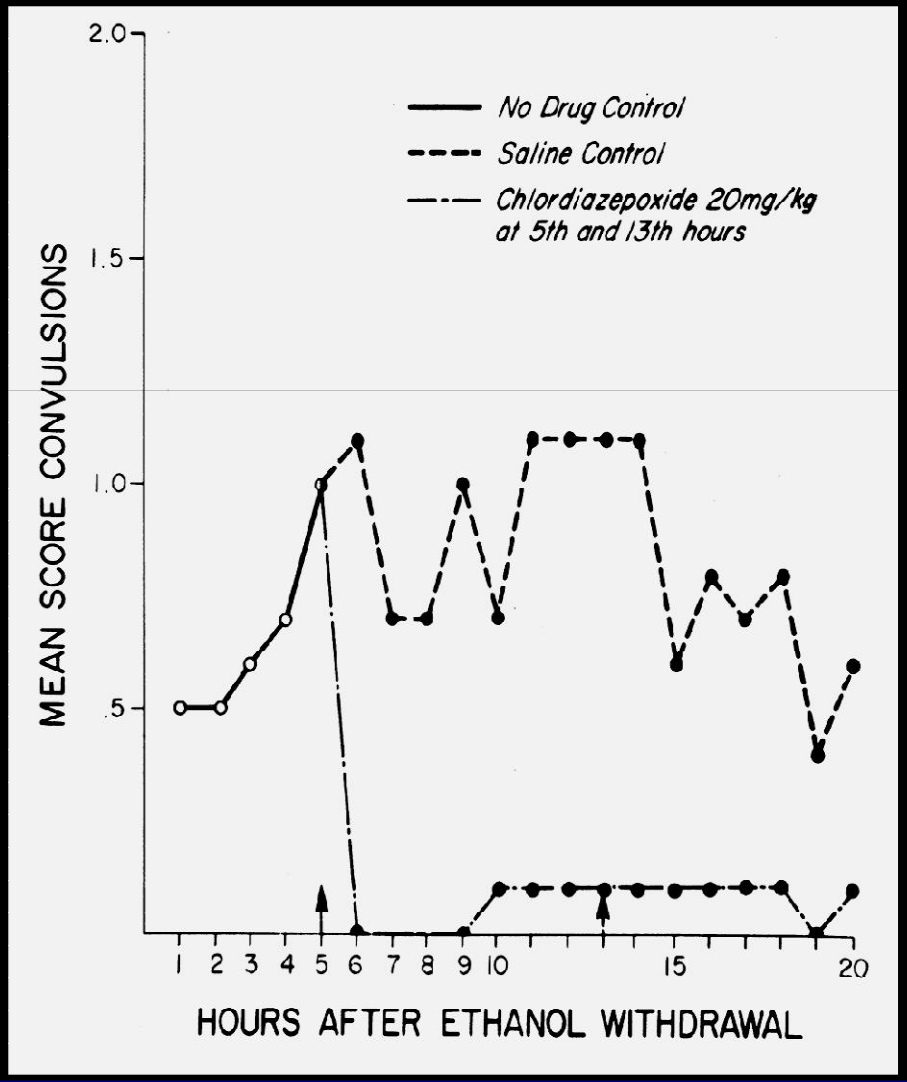
Morrow: J Pharmacol Exp Ther 1988:246:158

Phenytoin for Withdrawal Seizures

- 90 patients with alcohol related seizures
- Random assignment to phenytoin (1gm) or placebo
- End points
  - Seizure recurrence
  - 12 hour seizure free period
- No benefit demonstrated with strong power analysis (14%)

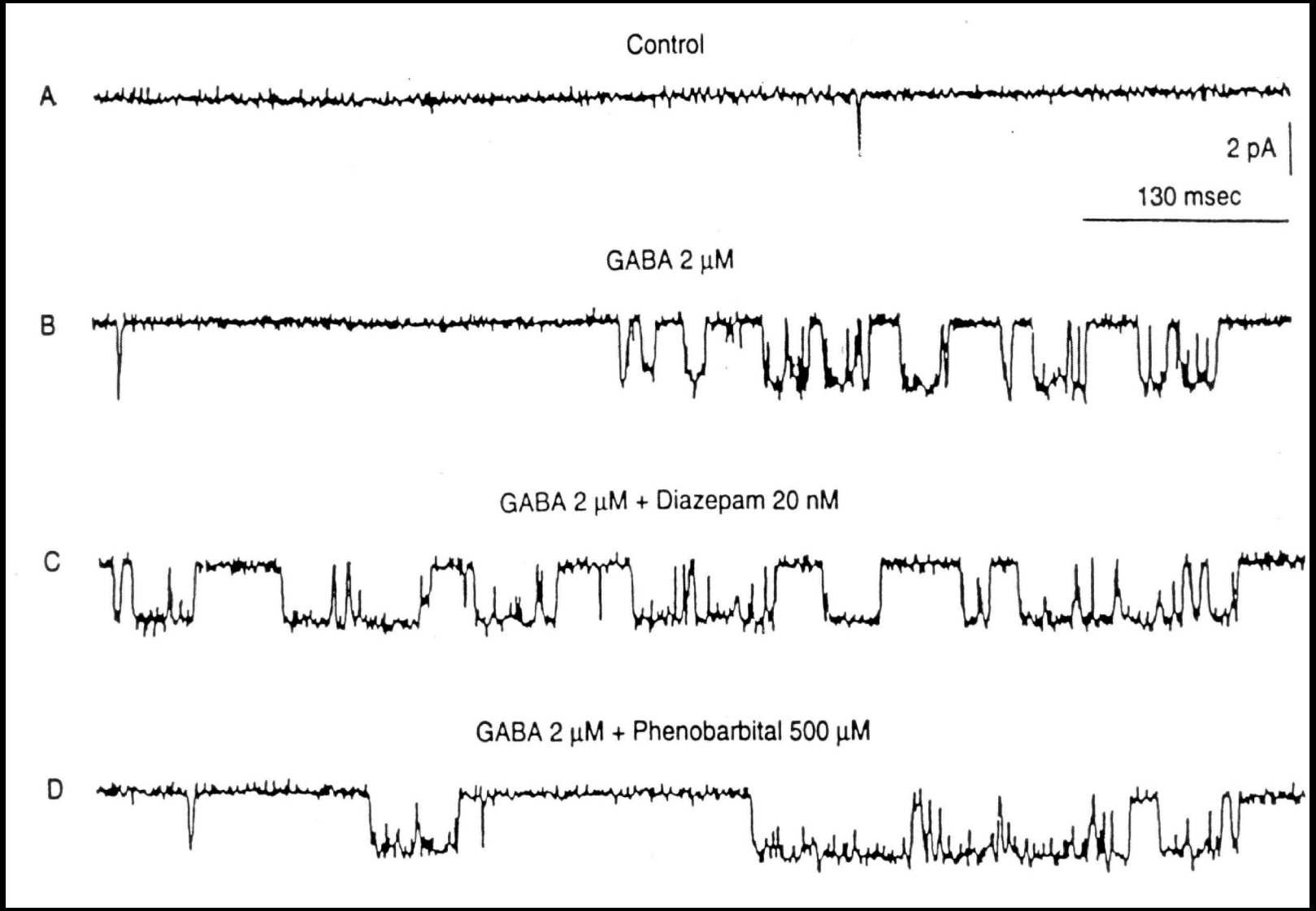
Alldredge: Am J Med 1989;87:645

Chlordiazepoxide



Blum: J Toxicol 1976;3:427

Synergy (BZ + PB)



Twyman: Ann Neurol 1989;25:213

LORAZEPAM FOR THE PREVENTION OF RECURRENT SEIZURES RELATED TO ALCOHOL

N Engl J Med 1999;340:915-9

GAIL D'ONOFRIO, M.D., NIELS K. RATHLEV, M.D., ANDREW S. ULRICH, M.D., SUSAN S. FISH, PHARM.D., M.P.H., AND ERIC S. FREEDLAND, M.D.

- 186 patients with EtOH withdrawal seizures randomly assigned to receive 2 mg of lorazepam or placebo
- Lorazepam
  - 3 of 100 patients (3 percent) had a second seizure
- Placebo
  - 21 of 86 patients (24 percent) had a second seizure
- Odds ratio for seizure with the use of placebo, 10.4; 95 percent confidence interval, 3.6 to 30.2; $P<0.001$)

J. Med. Toxicol. (2011) 7:16–23
DOI 10.1007/s13181-010-0096-4

TOXICOLOGY INVESTIGATION

Risk Factors for Complications of Drug-Induced Seizures

Josef G. Thundiyil · Freda Rowley · Linda Papa · Kent R. Olson · Thomas E. Kearney

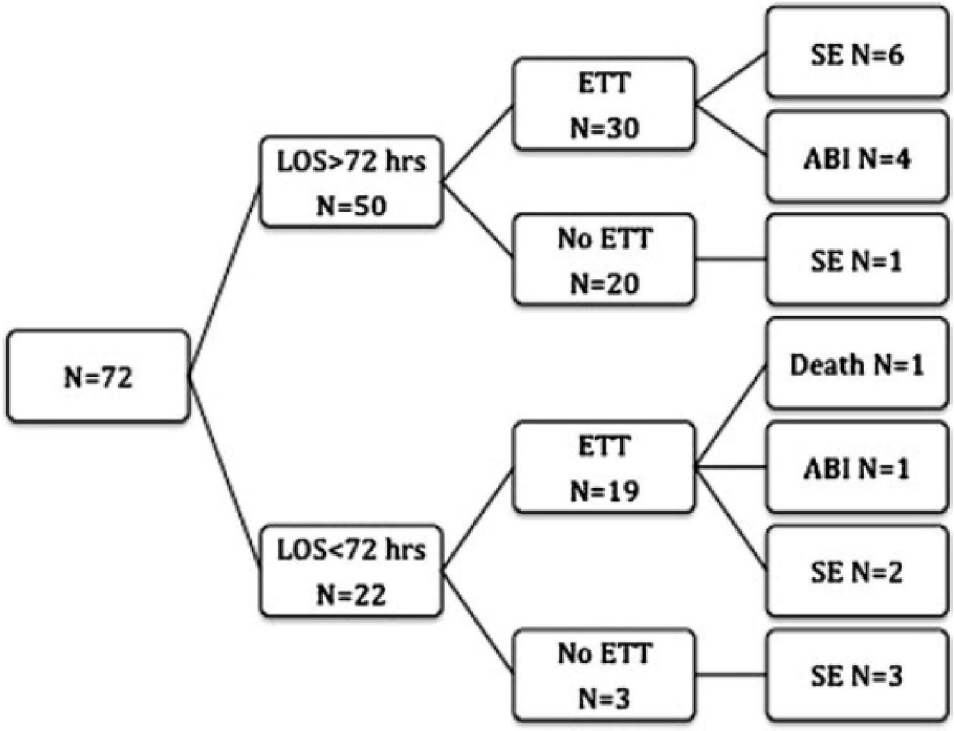
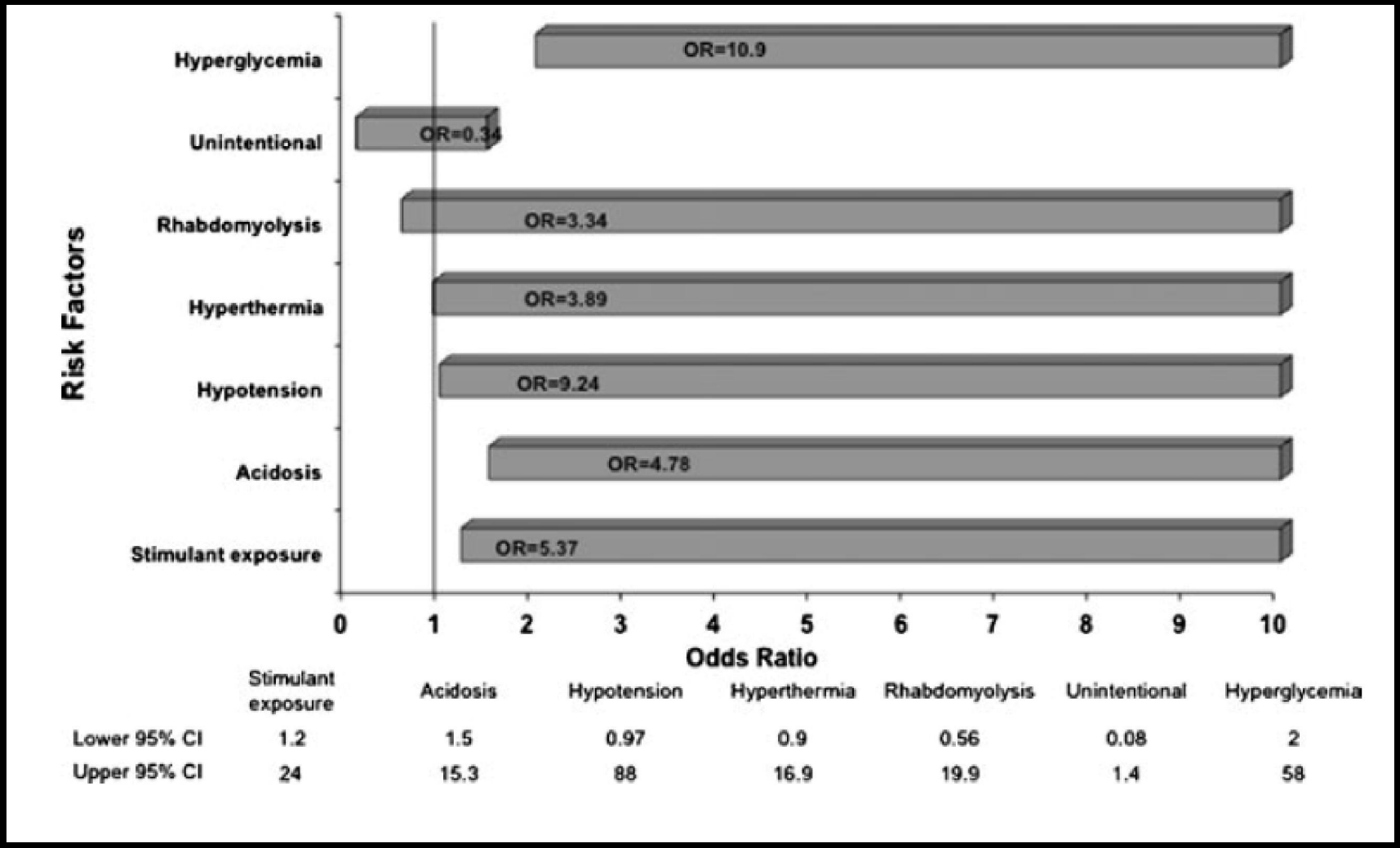


Fig. 1 Breakdown of study patients with complications. *LOS* length of stay, *ETT* endotracheally intubated, *SE* status epilepticus, *ABI* anoxic brain injury



	Stimulant exposure	Acidosis	Hypotension	Hyperthermia	Rhabdomyolysis	Unintentional	Hyperglycemia
Lower 95% CI	1.2	1.5	0.97	0.9	0.56	0.08	2
Upper 95% CI	24	15.3	88	16.9	19.9	1.4	58

Problem Seizures

- Definition:
  - Seizures that respond to anticonvulsants but the patient is still at risk
- Considerations:
  - Hypoglycemia (various)
  - Hyponatremia (XTC)
  - Carbon monoxide

Summary

- Try to define the etiology
- Always start with a benzodiazepine
- Avoid phenytoin
- Think about antidotes
- Add barbiturates for synergy
  - Think about anesthetic barbiturates
- Rapid airway protection
- Consider early NMB with EEG monitoring