ANTIDEPRESSANT PHARMACOLOGY AND TOXICITY:

TRICKS OF THE TRADE.

Will Rushton, MD
Associate Professor

Medical Director
Alabama Poison Information Center
Children's of Alabama

Director, Office of Med Tox
Department of Emergency Medicine
University of Alabama Birmingham

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PEDIATRICS

2024 CHILDREN'S OF ALABAMA APP PHARMACOLOGY CONFERENCE

MARCH 8, 2024

Please note: William Rushton, MD

Does not intend to discuss commercial products or services.

Does not intend to discuss non-FDA approved uses of products/providers of services.

Does not have a relevant financial arrangement or affiliation with any ineligible companies.

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GOALS

1. Debate the best channelopathies and discuss why the GABA-A channel is the clear favorite.

2. Review antidepressant toxicities

3. Explore mitochondria toxins

3

….Also known as how I came to love the GABA-A chloride ionophore channel

4

REMEMBER THREE THINGS IN TOXICOLOGY:

1. Check a level

2. Give some benzos. Then give some more.

3. Give some bicarb

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"There are very few toxicological problems that cannot be solved through the suitable (and liberal) application of benzodiazepines"

Suzanne White, MD

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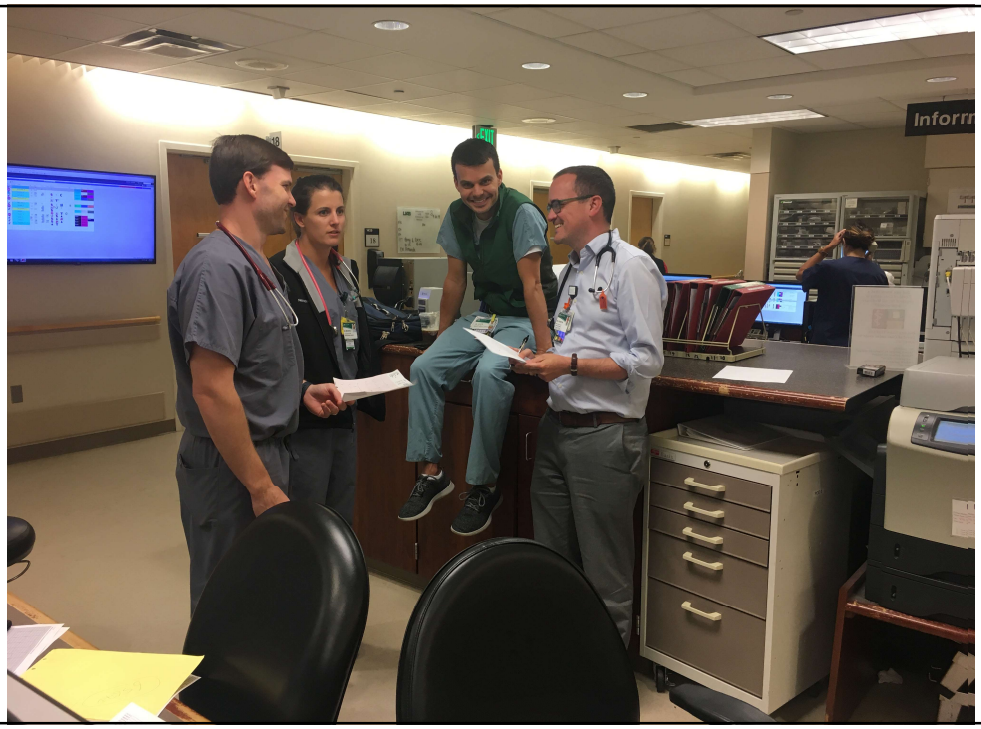

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CASE 1

A 30 yo female presents by ambulance. An empty bottle of phenobarbital and diazepam was found at the scene.

She is moderately arousable initially but continues to decompensate.

You fear for her airway.

Management?

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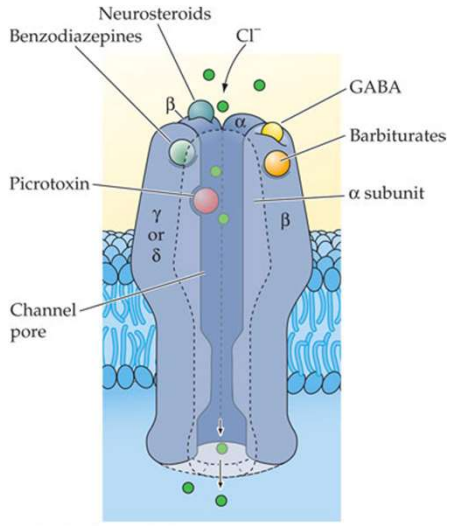

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GABA-A TOXICITY

- Nonspecific
- **CNS: drowsiness, dizziness, slurred speech,**
- nystagmus, confusion, ataxia, coma (rare)
- Children: 17% isolated ataxia (benzodiazepines)
- Other: respiratory depression (**rare in single benzo ingestions**), hypotension with IV administration

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GABA-A AGONISTS - BENZOS

- All are indirect agonists at post-synaptic GABAA channels
- **Can't open the channel without GABA**
- BZD1 receptors
  - **Increase frequency of Cl channel opening**
- BZD2 receptors (spinal cord) affect muscle relaxation
- All produce tolerance with cross-reactivity

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GABA-A AGONISTS - BARBITURATES

- Direct increase in **duration** of channel opening
- **GABA not needed**
- 4 Categories
  - Ultrashort: methohexital, thiopental
  - Short: pentobarbital, secobarbital
  - Intermediate: butalbital
  - Long-acting: phenobarbital
- CYP450 induction: drug interactions

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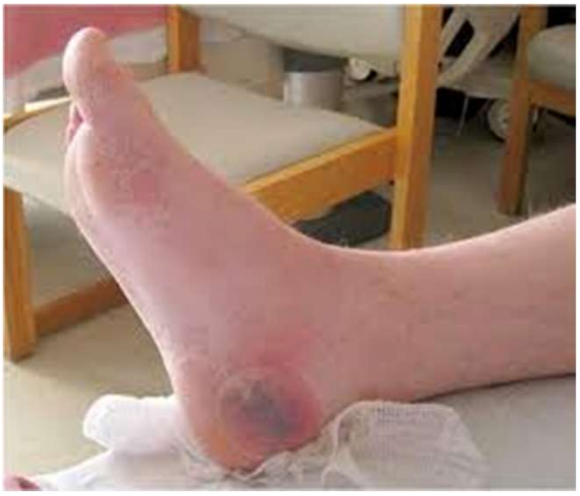
"BARB BURNS"



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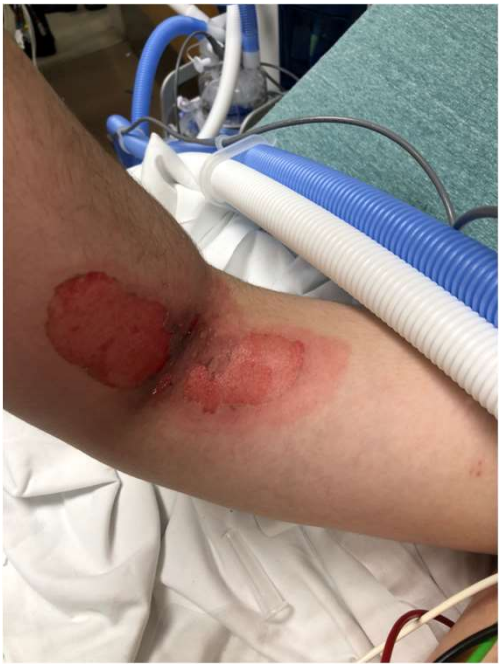

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THERAPEUTIC TRENDS IN THE TREATMENT OF BARBITURATE POISONING: THE SCANDINAVIAN METHOD

C. Clemmesen and E. Nilsson

Psychiatric Department, Bispebjergs Hospital and University Hospital of Lund, Copenhagen, Denmark and Lund, Sweden

Clin. Pharmacol. & Therap., *2:* 220–229, March–April, 1961

The technique today called the "Scandinavian method" for the therapy of barbiturate poisoning is an outgrowth of the earlier approaches employing gastric lavage and intensive use of central analeptics. The abandonment of these approaches, and the institution of rigid control of homeostasis of all systems in the poisoned individual have produced a mortality rate of 1 to 2 per cent, as compared to previous reports of up to 20 per cent. Since it utilizes no massive doses of analeptics, this approach has been labeled pharmacotherapeutic nihilism, a term which the authors decry by pointing to their current survival rate.

Essentially, the barbiturate-poisoned individual goes through 3 stages of clinical development following ingestion. These are the induction phase, produced by the immediate effects of the poison (*e.g.* shock), the second or coma phase, in which physiologic balance has been established but must still be rigidly maintained, and the third or reawakening phase, in which gradual return to normal occurs again under strict supervision.

The chief causes of death occur through complications arising from the circulatory, respiratory and renal systems. These causes account for nearly 80 per cent of the deaths. Therefore, chief attention is focused on these 3 systems.

Shock results from the effect of the barbiturate on the vasomotor center and on the myocardium itself. Immediate attention is thus given to transfusion of blood, dextran, or plasma. If such therapy is not adequate, shock is then combatted with intravenous vasopressor drugs to stabilize blood pressure and to prevent subsequent renal damage with anuria. Corticosteroids have been used, but without appearing to influence the outcome.

Respiratory management is directed toward the prevention of anoxia by maintaining a clear airway, and to the prevention of infection and atelectasis. Antibiotics are administered prophylactically, oxygen is administered, daily X-rays checked for lung consolidation, atelectasis is treated with suction and bronchoscopy, and the patient is turned from side to side every 2 hours. The

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DRUG TESTING

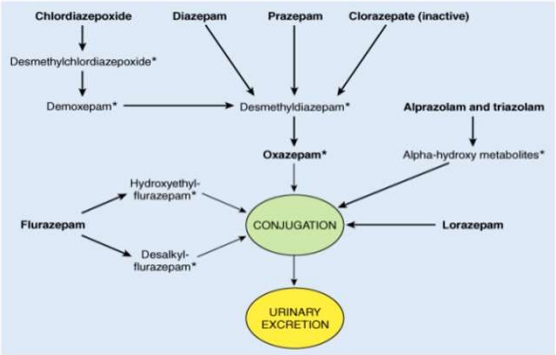

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Table 2. DRI Benzodiazepine Assay Cross-Reactivity Levels

Compound	Concentration, ng/mL
Alprazolam	105
7-Aminoclonazepam	2500
Bromazepam	225
Chlordiazepoxide	1100
Clobazam	145
Clonazepam	500
Clorazepate	120
Delorazepam	110
Desmethyldiazepam	100
Diazepam	95
Flunitrazepam	175
Flurazepam	140
Lorazepam	1000
Lormetazepam	225
Medazepam	225
Nitrazepam	175
Norfludiazepam	115
Prazepam	110
Temazepam	125
Triazolam	125

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CHLORAL HYDRATE

Commonly used by alcoholics in the late 19th century to induce sleep

Solutions of alcohol and chloral hydrate often called "knockout drops" or "Mickey Finn"

Hemorrhagic gastritis

Cardiac arrhythmias

Attributed largely to trichloroethanol

DRUGS TO THE NON-TIPPERS

ARRESTED CHICAGO WAITERS CONFESS POISONING HOTEL GUESTS.

Detectives Seize Large Quantity of "Mickey Finn" Powder at Headquarters of Servers' Union—"Reprisals" Were Numerous.

CHICAGO, June 23.—Four persons were arrested and more than one hundred waiters taken into custody by the state attorney's office today in connection with the alleged wholesale drugging of patrons of leading hotels, clubs and restaurants by waiters whose displeasure the patrons incurred when they neglected to leave a tip on the table after being served.

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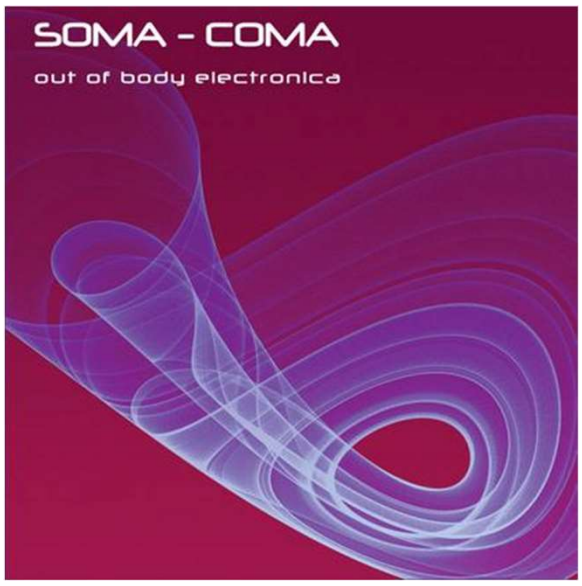
MEPROBAMATE (MILTOWN, EQUANIL, MEPROSPAN)

Active metabolite of carisoprodol

Concretions/bezoars in overdose



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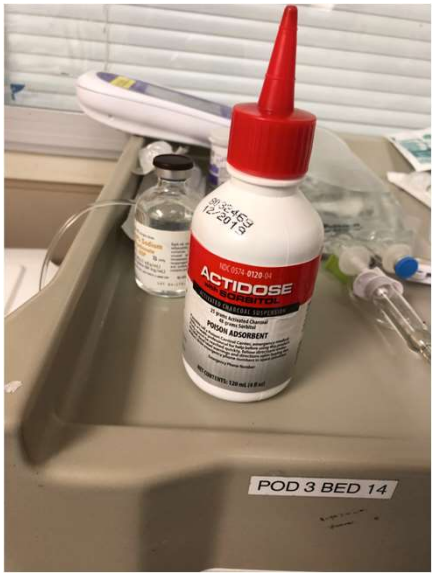
Slide 19

[2]1 wrushton@gmail.com, 12/14/2015



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SHE DID WHAT? (CASE 2)

A 14 yo female overdoses on bupropion XL and is immediately brought to the ED. She initially presents with a HR of 103 BPM, BP 125/80, and a RR of 20.

Disposition?

Treatment?

Mechanism?

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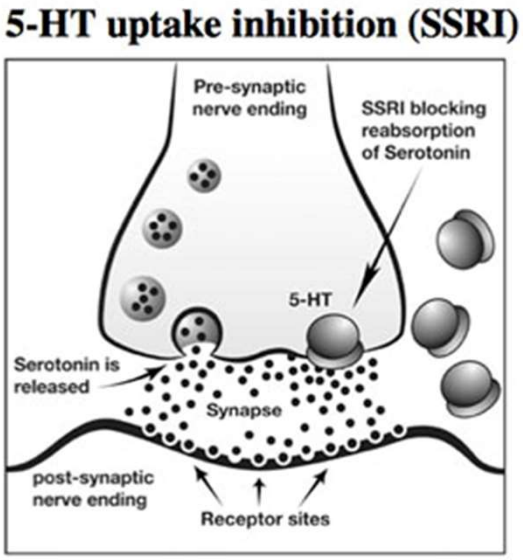
SSRIS

- Paroxetine
- Fluoxetine
- Citalopram
- Escitalopram
- Sertraline
- Fluvoxamine Fluoxetine + olanzepine (Symbyax)



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SNRI AND OTHERS

Buproprion

Excitation in overdose, SEIZURES, XL products

Mirtazepine

Sedation, mild symptoms in toxicity

Nefazadone, Trazadone

Prolonged QT, orthostatic hypotension, priapism

Venlafaxine

Seizures, QRS prolongation

Duloxetine

Mild sympathomimetic effects; generally low toxicity

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SEROTONIN SYNDROME

- Stimulation of post-synaptic 5HT1A and 5HT2a brain receptors
- Two or more serotonergic agents
  - SSRI + neuroleptic
  - SSRI + agent with serotonergic properties
  - Change in dose
  - Metabolic inhibition
- Triad:
  - Mental-status changes
  - Autonomic hyperactivity
  - Neuromuscular abnormalities

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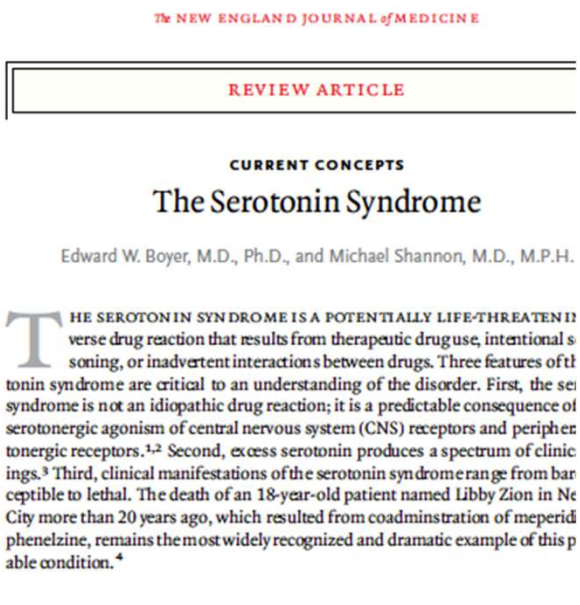
THE SEROTONIN SYNDROME



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

The Serotonin Syndrome

Edward W. Boyer, M.D., Ph.D., and Michael Shannon, M.D., M.P.H.

THE SEROTONIN SYNDROME IS A POTENTIALLY LIFE-THREATENI
verse drug reaction that results from therapeutic drug use, intentional s
soning, or inadvertent interactions between drugs. Three features of t
tonin syndrome are critical to an understanding of the disorder. First, the se
syndrome is not an idiopathic drug reaction; it is a predictable consequence of
serotonergic agonism of central nervous system (CNS) receptors and peripher
tonergic receptors.[1,2] Second, excess serotonin produces a spectrum of clinic
ings.[3] Third, clinical manifestations of the serotonin syndrome range from bar
ceptible to lethal. The death of an 18-year-old patient named Libby Zion in Ne
City more than 20 years ago, which resulted from coadminstration of meperidi
phenelzine, remains the most widely recognized and dramatic example of this p
able condition.[4]

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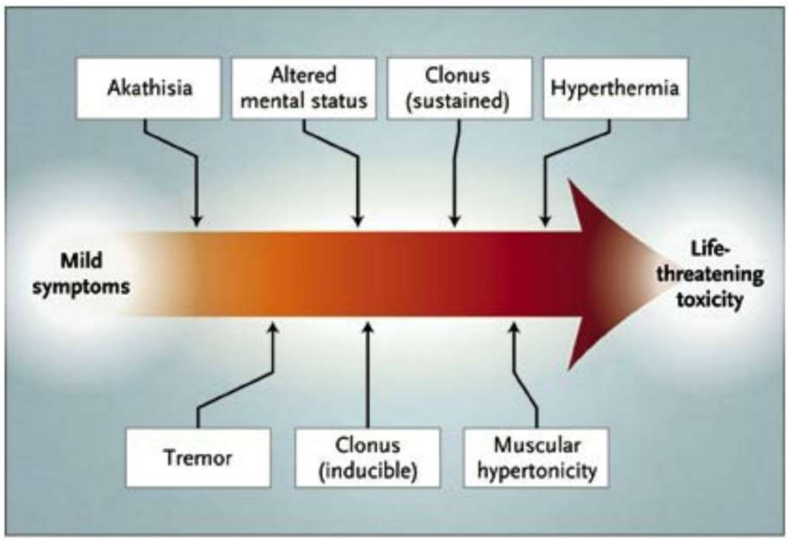
Akathisia
Altered mental status
Clonus (sustained)
Hyperthermia
Mild symptoms
Life-threatening toxicity
Tremor
Clonus (inducible)
Muscular hypertonicity

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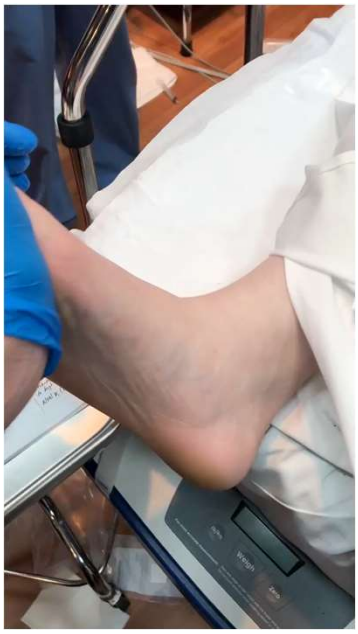

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ANTIDEPRESSANTS I CARE ABOUT

Bupropion
- Be wary IR vs SR vs XL

Venlafaxine

Citalopram

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PATRON SAINT OF RESIDENTS EVERYWHERE (CASE 3)

A 19 yo college freshman with a cocaine addiction is admitted to a NYC hospital after an overdose of suspected phenelzine (an MAOI) with fever, altered mental status, hyperthermia, and tachycardia. She is noted to have rigors and does not improve with IV hydration.

Initial Management?

How would you treat her rigors?

30

NOT ALL THAT CAUSES MIOSIS IS PERCOCET…(CASE 4)

A 40 yo male presents to the ED with EMS s/p ingestion of an unknown drug. His exam is notable for miosis, severe lethargy, tachycardia, RR of 16, HR of 120, and a BP of 90/40.

Differential?

Management?

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TYPICAL VS ATYPICAL ANTI-PSYCHOTICS

Typical

- Strong antagonism at the D2 receptor site
- Moderate blockade at the Muscarinic Receptor
- Example:
  - Haloperidol

Atypical

- Partial antagonism at D2 and blockade of 5HT-2a receptors
- Alpha-1 antagonism
- Blockade of potassium currents in cardiac myocytes
- Examples:
  - Aripiprazole
  - Quetiapine
  - Risperidone
  - Ziprasidone

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ATYPICAL ANTI-PSYCHOTICS…CONT

- Anti-Muscarinic
  - Olanzapine, Quetiapine
- Really Strong Alpha-1 antagonists
  - Quetiapine
- QT prolongers
  - Ziprasidone

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Disorder	Features	Mechanism	Treatments
Acute dystonia	Sustained, involuntary muscle contraction; torticollis	Imbalance of dopaminergic/cholinergic transmission	Anticholinergics/BDZ
Akathisia	Restlessness; inability to sit still	Mesocorticol D2 antagonism	Dose reduction / anticholinergics
NMS	AMS, hyperthermia, autonominc instability	D2 antagonism in the striatum	Cooling, BDZ, dopamine agonists
Tardive Dyskinesia	Late onset (months to years) involuntary choreiform movements	Excess dopaminergic toxicity	Stop offending agent

From Goldfranks 9th Edition: Antipsychotics

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Differential?

Management?

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From Goldfranks 9th Edition: Antipsychotics

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DANTROLENE IN NMS?

Research

Open Access

Managing an effective treatment for neuroleptic malignant syndrome

Udo Reulbach, Carmen Dütsch, Teresa Biermann, Wolfgang Sperling, Norbert Thuerauf, Johannes Kornhuber and Stefan Bleich

Department of Psychiatry and Psychotherapy, Friedrich Alexander University of Erlangen-Nuremberg, Schwabachanlage 6, D-91054 Erlangen, Germany

Corresponding author: Udo Reulbach, udo.reulbach@psych.imed.uni-erlangen.de

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This article is online at: http://ccforum.com/content/11/1/R4

Abstract

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WHERE DO PEOPLE GET THESE MEDICATIONS? (CASE 5)

A 17 yo male presents to the ED after overdose on an unknown "headache medication." His initial HR is 122, BP is 100/60, RR are 18, and temp is 37.8C. He appears moderately lethargic but is currently protecting his airway and his pupils are 6mm.

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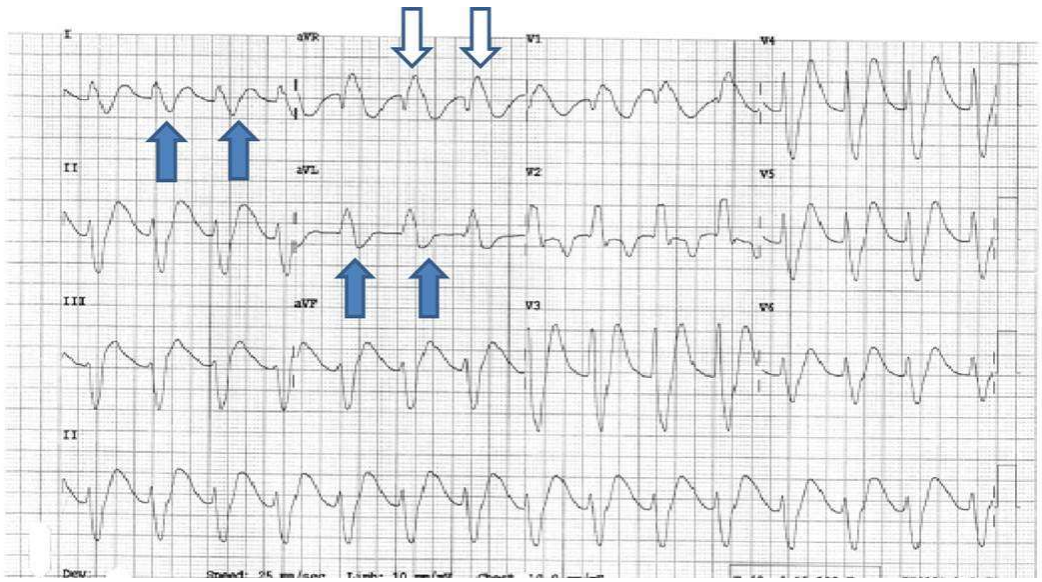

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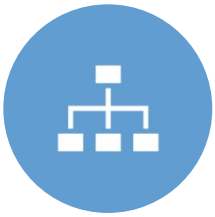
WHILE WAITING FOR HIS ICU BED, THE PATIENT STARTS SEIZING



MANAGEMENT?

CASE 5….CONT. THE CATASTROPHIC DECLINE.

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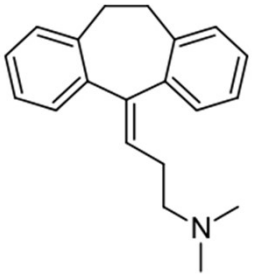
TRICYCLIC ANTIDEPRESSANTS

Tertiary amines

- Tertiary amines
- Amitriptyline
- Clomipramine
- Doxepin
- Imipramine
- Trimipramine

Secondary amines

- Desipramine
- Nortriptyline
- Protriptyline



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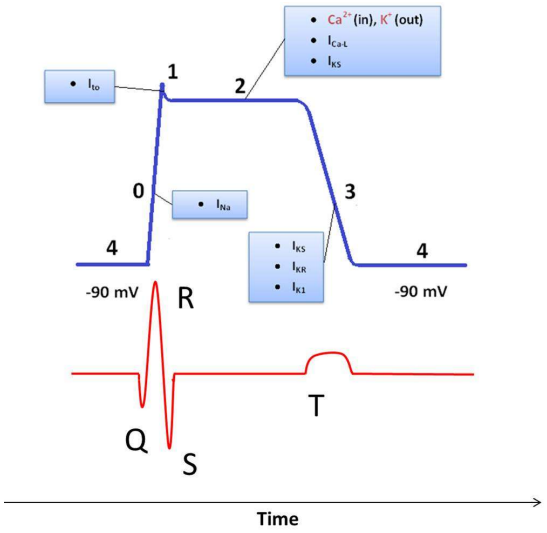
7 MECHANISMS OF TCA POISONING

1. Alpha 1 antagonism
2. Anti-muscarinic
3. Cardiac sodium channel blocker
4. Potassium efflux channel blocker
5. Anti-histamine
6. Anti-GABA channel (remember this from the beginning)
7. Biogenic amine reuptake inhibitor



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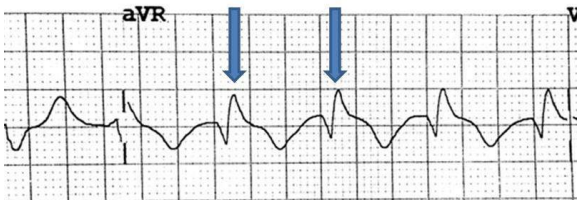
TREATMENT OF TCA TOXICITY

Hemodynamic stable patient
- Defer NaHCO3 treatment unless QRS > 120msec
- Serial EKG (q2 hours for the first 6 hours)
- Cardiac Monitoring
- 2 gm MgSO4 QTc > 500msec
- Replenishment of electrolytes

Hemodynamic unstable pt
- 2 amps (100meQ NaHCO3) regardless of QRS
- 150meq (3 amps) in 1LD5W at 1.5x maintenance
- Titrate arterial pH to 7.45-7.55 (don't forget about vent settings)
- Low dose norepi gtt for poor perfusion
- 2 gm MgSO4 for repeated dysrhythmias



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SEIZING TCA PATIENT – "CATASTROPHIC DECLINE"

1. GABA-agonist of choice

2. Immediate 100meq NaHCO3 with more as needed

3. Repeat EKG.

4. Intralipid therapy (1.5ml/kg of a 20% emulsion)

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TCA UDS POSITIVE

- Cyclobenzaprine (Flexeril)
- Diphenhydramine (Benadryl)
- Cyproheptadine (Periactin)
- Carbamazepine (Tegretol)
- Thioridazine (Mellaril)
- Quetiapine (Seroquel)

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CASE

24 yo male presented to the ER hypoxic, tachycardic, and hyperthermic after being found unresponsive at home. He was known to have a history of methamphetamine abuse.

SPO2 in the 60s. No response to naloxone. Intubated upon arrival. Temperature is 106F.

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ANCILLARY DATA

Unresponsive male, warm to the touch. Patient was noted to not be rigid on exam. HR 144, BP 117/67, RR 20bpm, temp 106F, 100% on ventilator.

Laboratory Data: Sodium 146 mEq/L, potassium 4.7 mEq/L, chloride 118 mEq/L, carbon dioxide 16 mEq/L, BUN 19 mg/dL, **creatinine 2** mg/dL

AST 291 U/L, ALT 68 U/L. EKG HR 167 , QRS 85 , QTc 324 .

Acetaminophen < 10 mcg/ml. Aspirin <1 mg/dl, ETOH < 10 mg/dl.

Lactic acid 4.4 mmol/L. UDS +benzodiazepines, +methadone.

ABG: pH 7.33, pCO2 27 HCO3 14.3. CK >8000units/L

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DIFFERENTIAL?

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TOXIC HYPERTHERMIA

Uncouplers of Oxidative Phosphorylation

Anticholinergics

Metal fume Fever

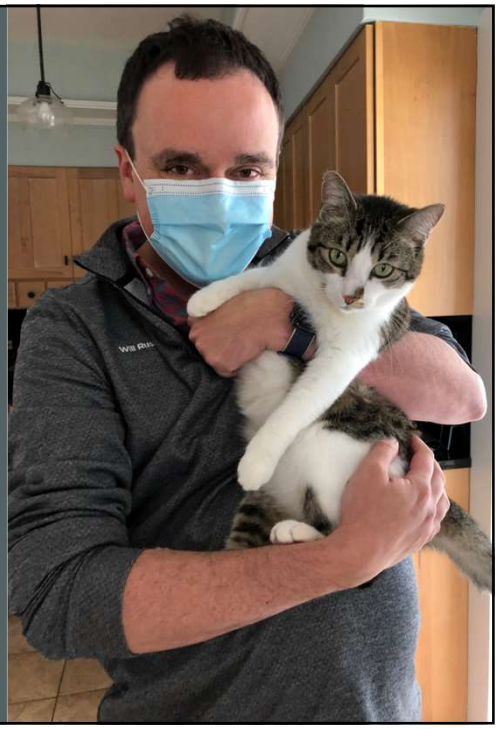
Malignant Hyperthermia

Serotonin Syndrome

Neuroleptic Malignant Syndrome

Endocarditis

Others…..



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TOXIC HYPERTHERMIA

Uncouplers of Oxidative Phosphorylation

Anticholinergics

Metal fume Fever

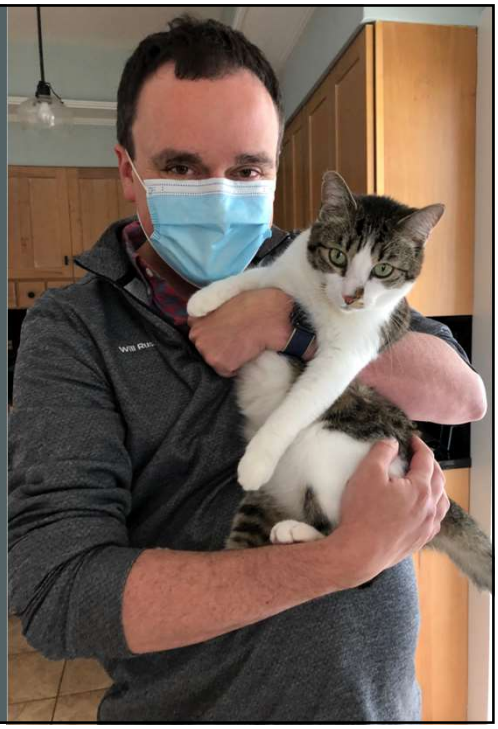
Malignant Hyperthermia

Serotonin Syndrome

Neuroleptic Malignant Syndrome

Endocarditis

Others…..



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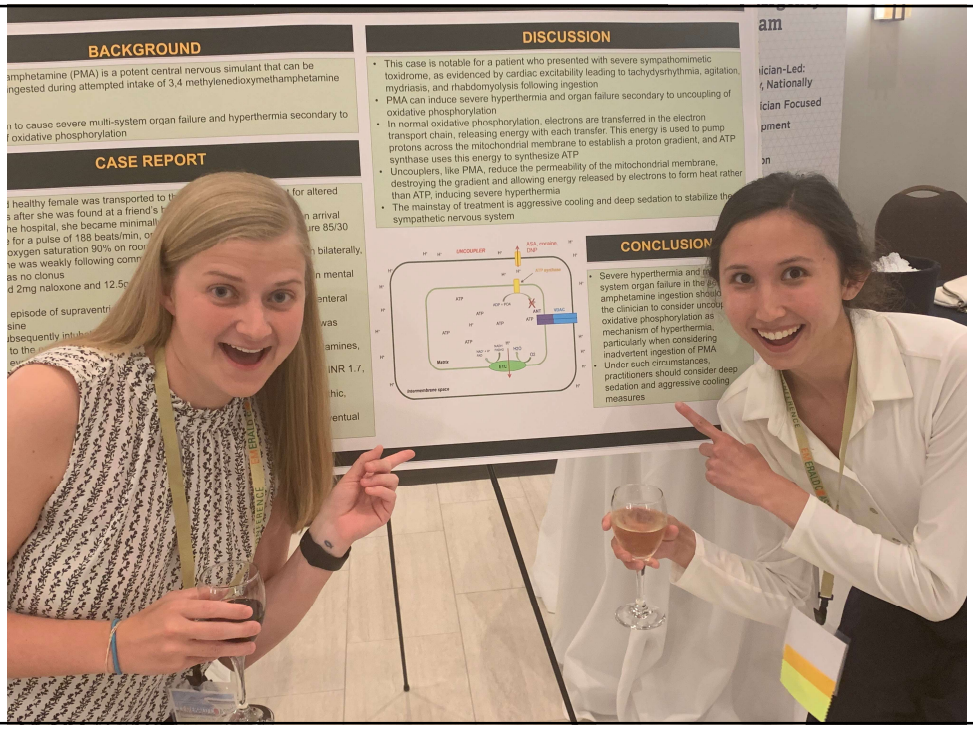
BACKGROUND
CASE REPORT
DISCUSSION
CONCLUSION

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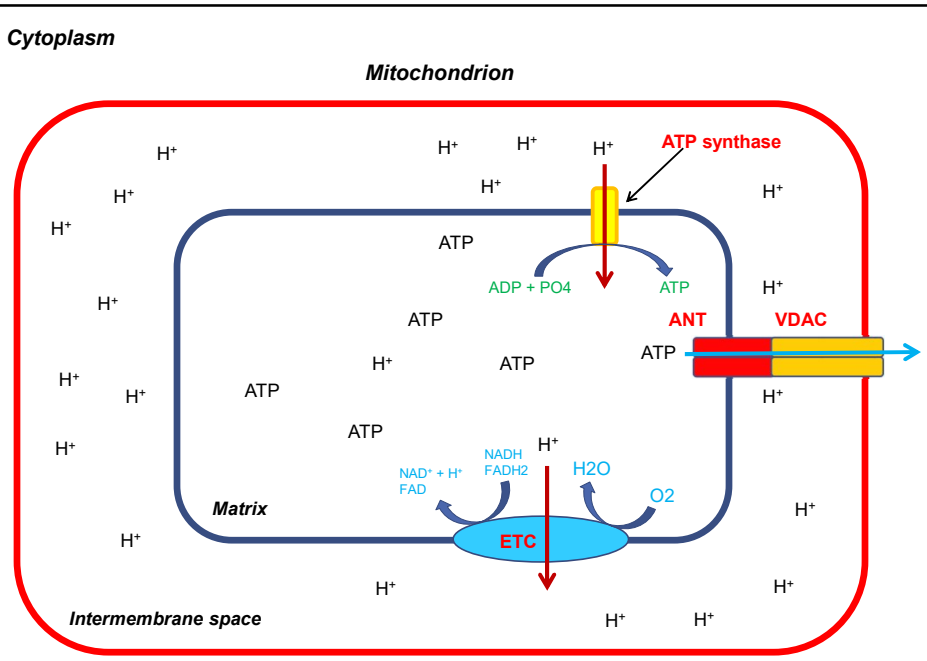
Cytoplasm
Mitochondrion
ATP synthase
ADP + PO4
ATP
ANT
VDAC
NADH
FADH2
NAD+ + H+
FAD
H2O
O2
ETC
Matrix
Intermembrane space

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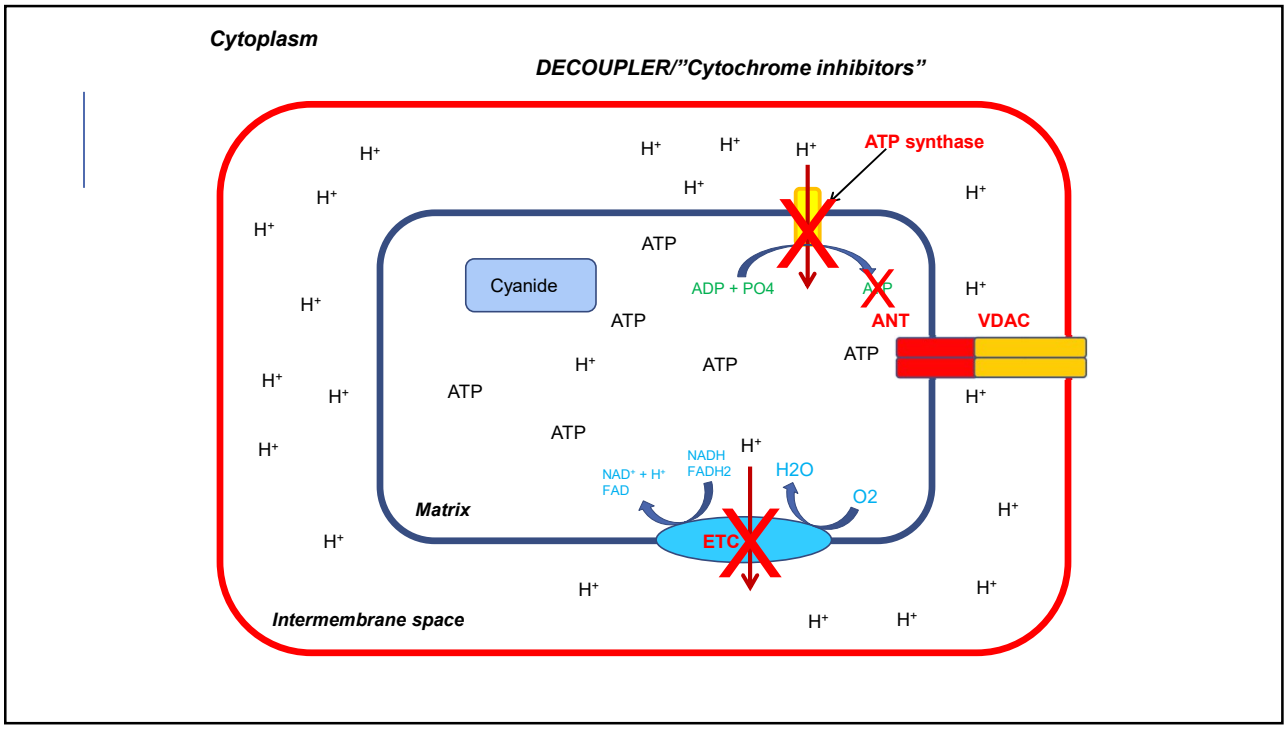
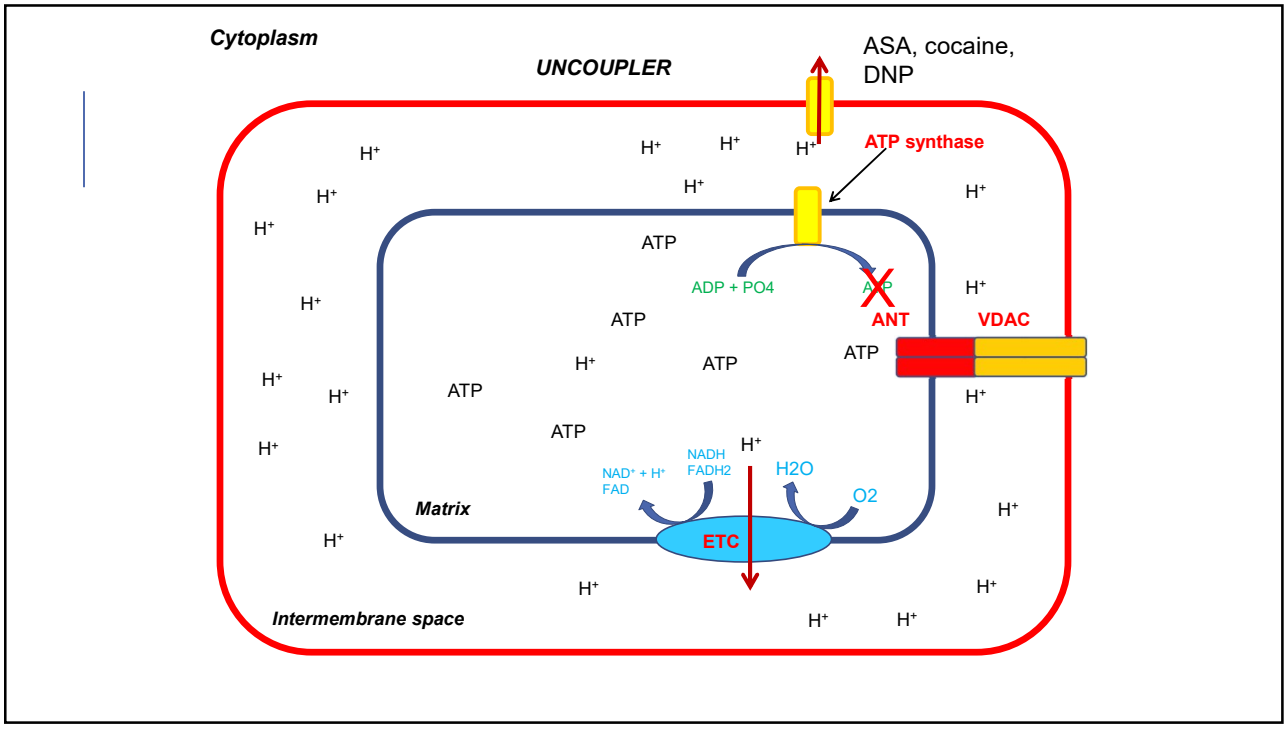

Cytoplasm
DECOUPLER/"Cytochrome inhibitors"
ATP synthase
Cyanide
ADP + PO4
ATP
ANT
VDAC
NADH
FADH2
NAD+ + H+
FAD
H2O
O2
ETC
Matrix
Intermembrane space
H+

53


Cytoplasm
UNCOUPLER
ASA, cocaine,
DNP
ATP synthase
ADP + PO4
ATP
ANT
VDAC
NADH
FADH2
NAD+ + H+
FAD
H2O
O2
ETC
Matrix
Intermembrane space
H+

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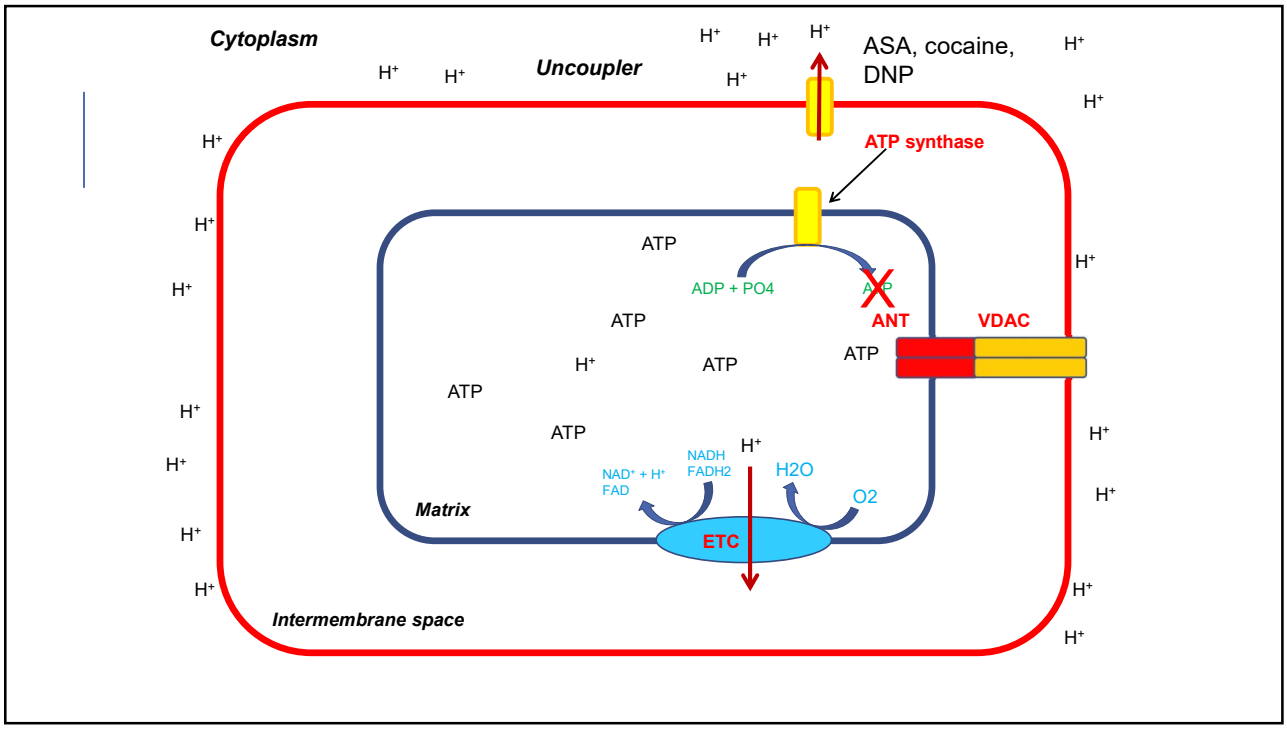
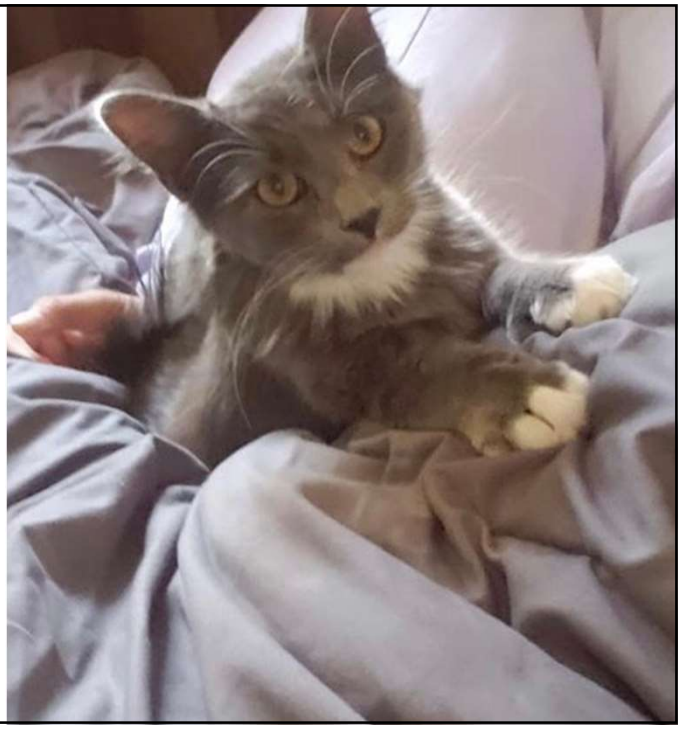

Cytoplasm
Uncoupler
ASA, cocaine, DNP
ATP synthase
ATP
ADP + PO4
ATP
ANT
VDAC
Matrix
NADH
FADH2
NAD+ + H+
FAD
H2O
O2
ETC
Intermembrane space
H+

55



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MALIGNANT HYPERTHERMIA

classic signs of MH include:

hyperthermia to marked degree, tachycardia,

tachypnea,

increased carbon dioxide production,

increased oxygen consumption,

acidosis,

muscle rigidity,

rhabdomyolysis.

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THE END.

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