Dancing with Death: MDMA, PMMA and other 4 letter words

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Objectives

- At the conclusion of this presentation, participants should be able to:
  - Appreciate the structural similarity between MDMA, PMMA and other amphetamines
  - Compare and contrast the clinical features of acute toxicity from MDMA, PMMA and other amphetamines
  - Describe the management of toxicity from MDMA, PMMA and other amphetamines

Outline

- Case presentation
- Background
- Pharmacology
- Pathophysiology
- Clinical features
- Management
- Summary

Case

- 16 y.o. male at house party
- Overnight: ingested “8 Ecstasy pills”
- Not seen for several hours
- Next day: walking outside house, bizarre behavior → unconscious, unresponsive
- Paramedics arrive: cardiac arrest X 1 en route to hospital → successfully resuscitated

Hospital course

- Arrives in ED ~ 1330 hours:
  - –temp 43^{o}C, GCS 3, sweaty, rigid
  - – arrests again → resuscitated
- Labs 1400 hours:
  - – K 9.6, lactate 3.7, CK 731, Creat 141, ALT 57, Tnt 0.03
- Treatment:
  - – admitted to ICU
  - – sedated and paralyzed
  - – cooling blankets, ice, cooling catheter

Hospital course

- Temperature normalized after 12 hours of active cooling
- Develops:
  - Rhabdomyolysis
  - Kidney and liver failure
  - Cerebral edema
- Died 4 days after admission

Comprehensive urine drug screen results

- Cannabinoids
- Amphetamine
- Methamphetamine
- MDMA
- PMA
- PMMA

Background

MDMA

- 3,4-methylenedioxymethamphetamine
- 1912 - first synthesized by Merck
- 1914 - marketed as appetite suppressant
- 1970’s/80’s - prescribed by psychotherapists to help patients “search within themselves”
- 1980’s – popularity at raves increases
- Street names: “Ecstasy”, “X”, “E”, “Adam”, “Molly”, “XTC”, “M&M”, “MDM”, “rolls”, “beans”

PMMA/PMA

- PMMA: Paramethoxymethamphetamine
- PMA: Paramethoxyamphetamine
- 1973 – PMA fatalities in Ontario
- 2011/12 – PMMA fatalities in AB and BC
- Street names: “Chicken Fever”, “Killer”, “Double stacked”, “Mitsubishi turbo”, “Red Mitsubishi”, “Death”, “Dr. Death”

Locations of PMMA fatalities worldwide

Pure Ecstasy?

- MDMA
- MDA
- MDEA
- MBDB
- mephedrone
- 2C-B
- atropine
- methamphetamine
- PCP
- pseudoephedrine

- caffeine
- lidocaine
- procaine
- ketamine
- DXM
- DOB
- PMA
- PMMA
- cocaine

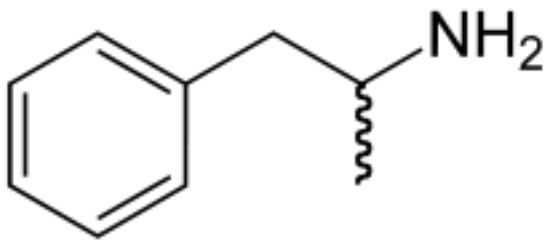
MDMA:

0 - 250 mg per tab

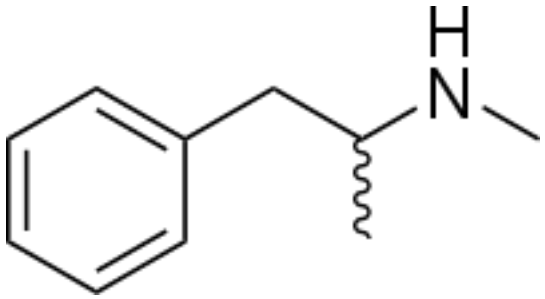
Togni et al. J For Sci 2015; 60: 147-151
Morefield et al. Addiction 2011: 106:1293-1300
Vogels et al. Addiction 2009; 104: 2057-2066

Pharmacology

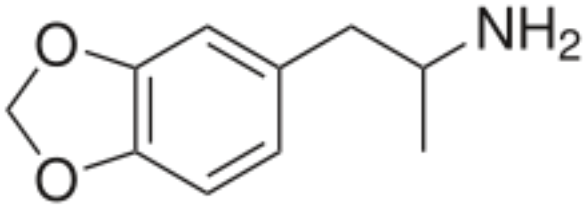
Structural similarities



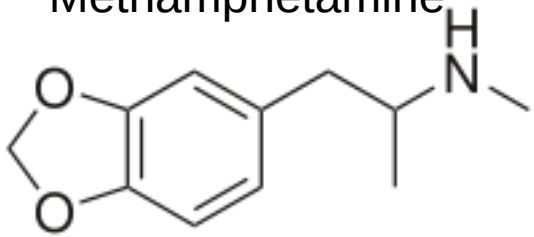
Amphetamine



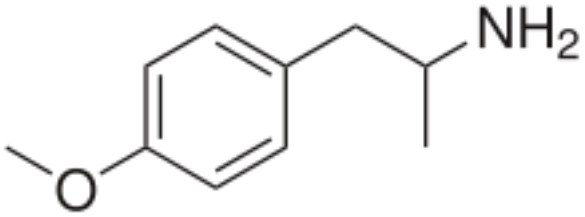
Methamphetamine



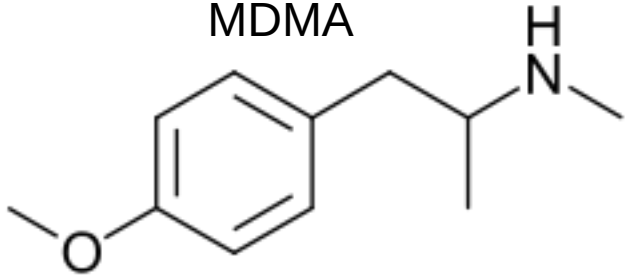
MDA



MDMA



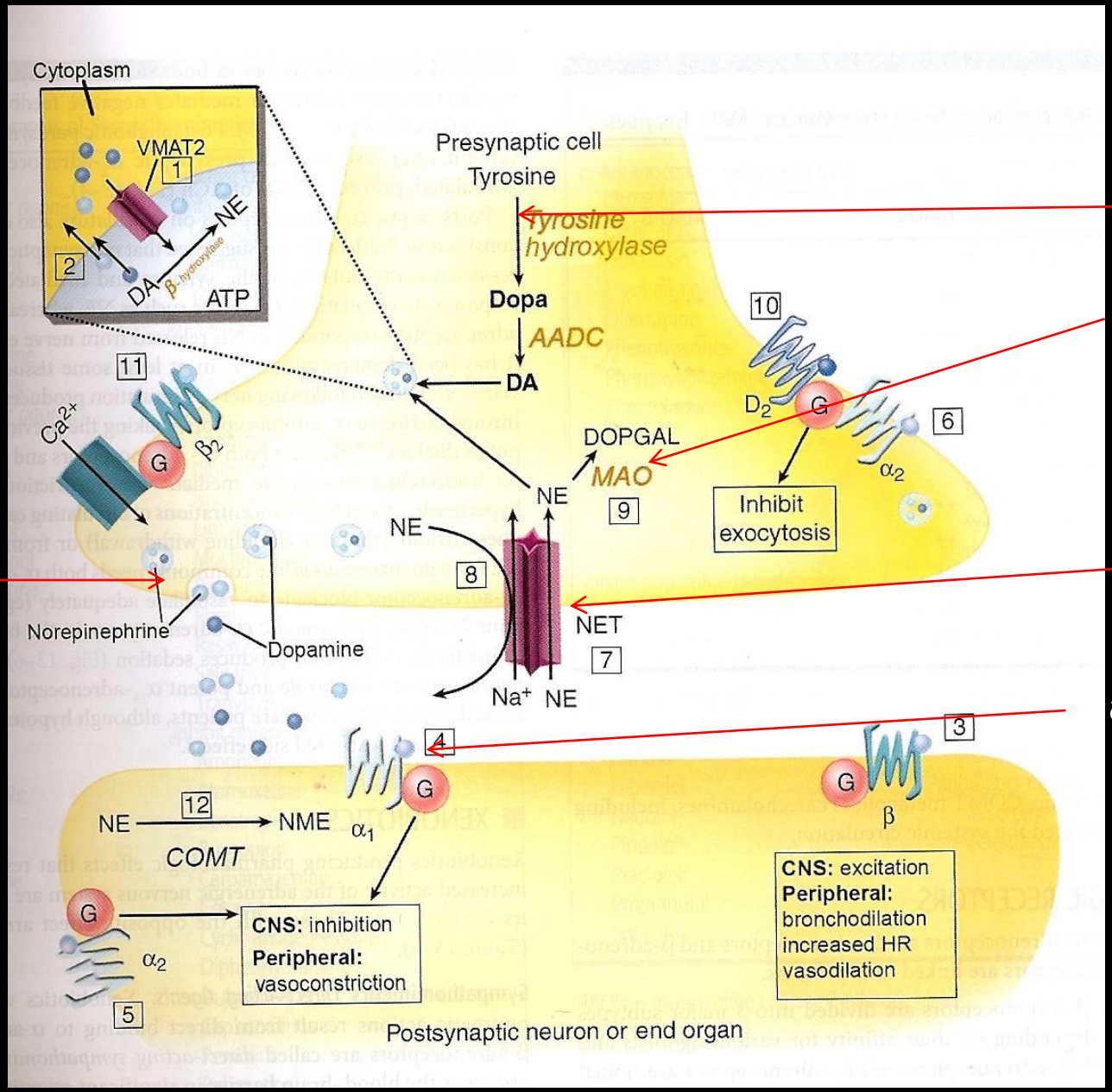
PMA



PMMA

MDMA: mechanisms of action

- Major:
  - release of norepinephrine and serotonin from presynaptic terminals
- Minor:
  - release of dopamine from presynaptic terminals
  - inhibit reuptake of catecholamines via competitive inhibition
  - monoamine oxidase inhibition



synthesis

breakdown

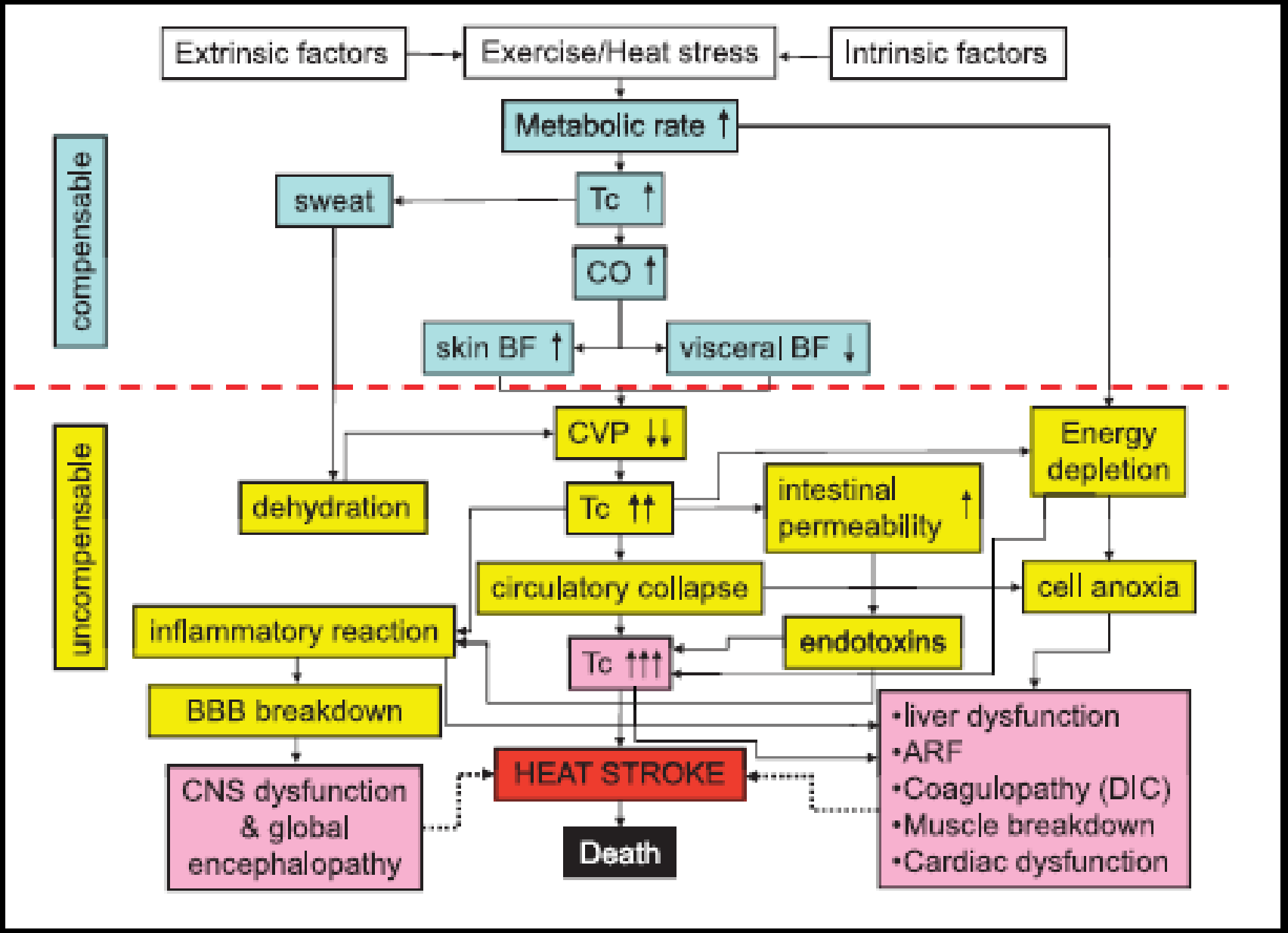
release

reuptake

agonism

Goldfrank's Toxicologic Emergencies, 9th ed, 2011, page 195

Pathophysiology



Epstein et al. Scand J Med Exer Sport 2011;21:742-8.

MDMA and heat generation

- Multifactorial
  - Drug dose
    - “the dose makes the poison”
  - Genetics
    - ? Ryanodine receptor dysfunction
    - ? Poor 2D6 metabolism
  - Hydration status
    - Activity, fluid consumption
  - Environment
    - Dance club, house, rave (“chill out room”), ambient temperature

Parrott et al. Drug Alc Dep 2012;121:1-9

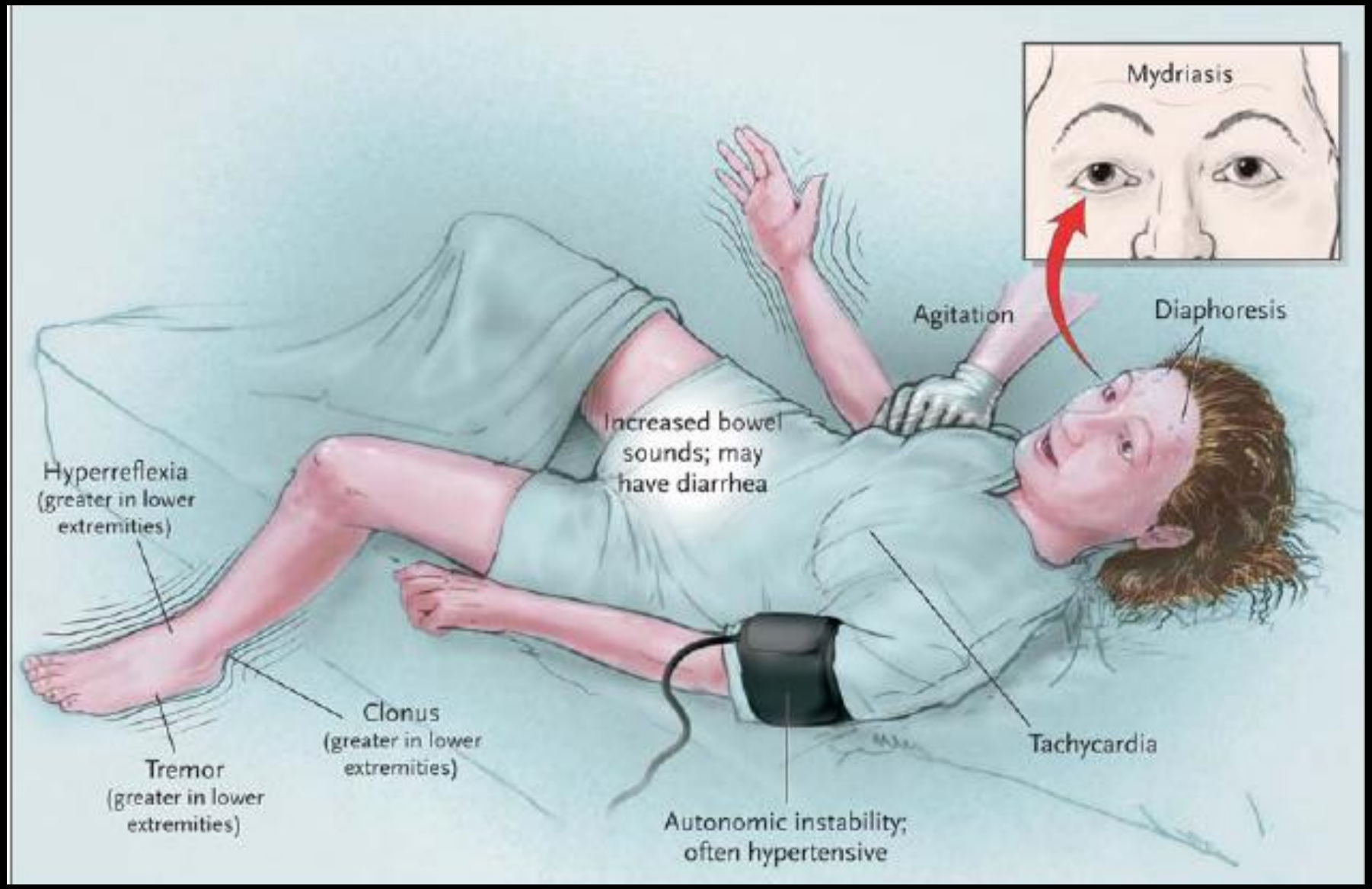
MDMA clinical features

Acute clinical features

- Serotonergic
- Sympathomimetic
- Dopaminergic

Serotonin Syndrome Clinical Triad

- Cognitive Changes
  - Altered mental status, elevated mood
- Autonomic Instability
  - Hyperthermia, high or low BP, tachycardia, mydriasis
- Neuromuscular Abnormalities
  - Clonus (spontaneous or inducible, wrist/ankles/eyes), hyperreflexia, rigid extremities, shivering, startling



Boyer et al, NEJM 2005;352:1112-20.

Sympathomimetic toxidrome

- Vitals: tachycardia, hypertension, hyperthermia
- Mental status: agitated
- Pupils: mydriasis
- Skin: diaphoretic
- Bowel sounds: normal or increased
- Misc: tremor, seizures

Dopaminergic effects

- Psychosis
- Choreoathetotic movements

PMMA toxicity

- Compared to MDMA:
  - Delayed onset of symptoms
  - Higher incidence of seizures and dysrhythmias
  - Hypoglycemia (reasons unclear)
  - ? Sodium channel blockade → wide QRS

AB and BC PMMA fatalities 2011-12

Characteristic	**Result (N=27)**
Median age, years	24 (range 14-52)
History of drug use, no. (%)	12 (44)
Time from exposure to death, hours	17 (5-264)
Median temperature on presentation, ^{o}C	39.4 (34-43.8)
Substances other than PMMA found in patient at death	MDMA (27), cocaine (14), methamphetamine (12)
Location of exposure	Home (13), house party (9), bar/concert (5)

Nicol et al. CMAJ Open 2015;3(1):E83-90.

Management

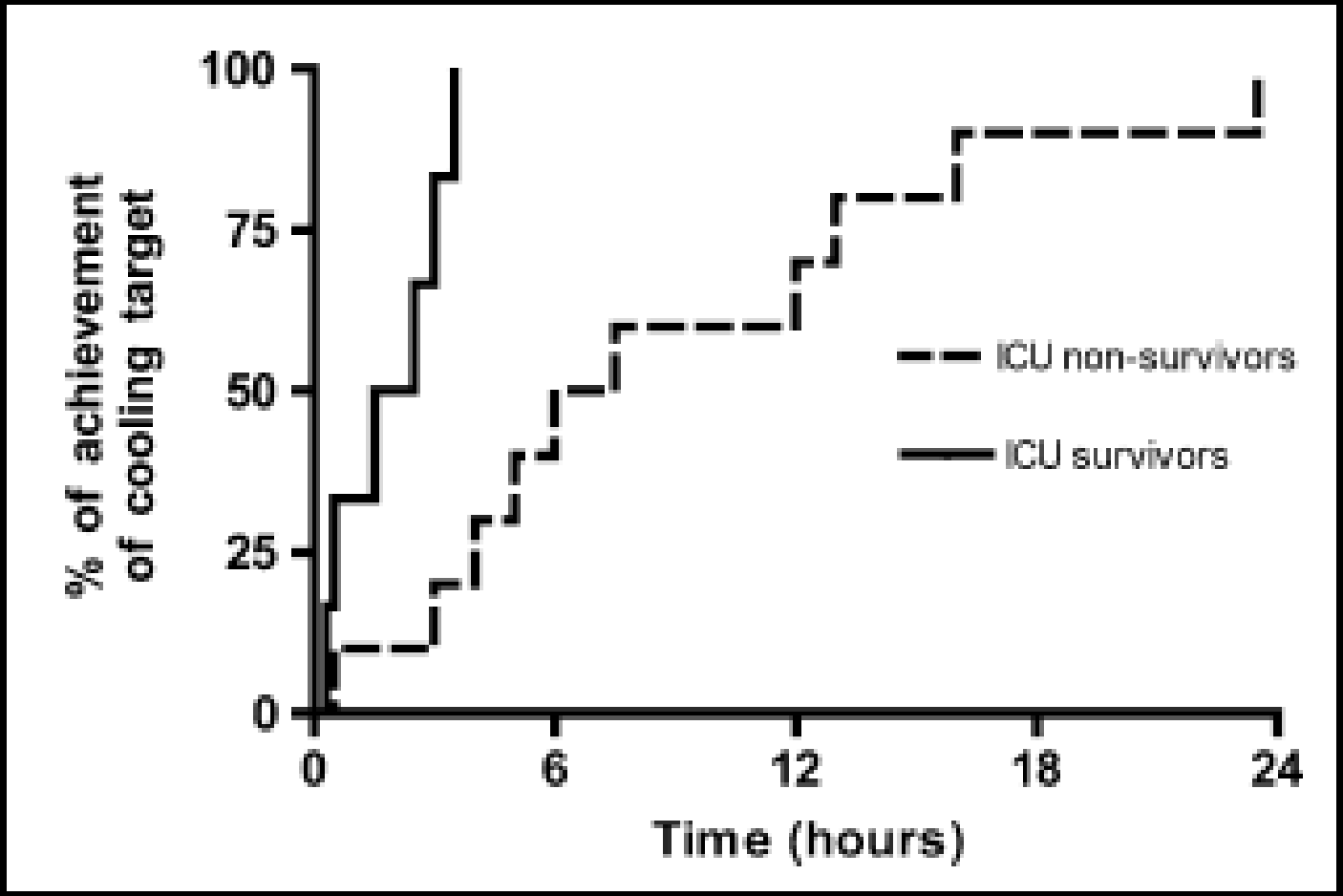
ABCDEFG's of toxicology

- **A**irway
- **B**reathing
- **C**irculation
- **D**econtamination
- **E**limination
- **F**ind an antidote
- **G**eneral management

Hyperthermia management

- Goal: core temp. < 39 degrees C
  - Benzodiazepines for agitation and shivering
  - Ice packs
  - Cooling blankets
  - Intubate, sedate and paralyze
  - Cooled IV Fluids (at 4°C)
  - Intravascular Cooling Devices
  - Specific antidotes
    - cyproheptadine, dantrolene

Cool it!



Pease et al. Int Care Med 2009;35:1454-1458.

Prognosis

- Predictors of outcome:
  - Degree and duration of temperature elevation
  - Longer time to initiation of cooling measures
  - Multiorgan dysfunction (anuria, coma, CV failure)
- Serial exams and serial imaging important

Take home points

- Variable content of street drugs
- Structural similarity between MDMA and PMMA results in similar clinical effects
- Clinical triad: adrenergic, serotonergic, and dopaminergic effects
- Rapid cooling and control of agitation mainstays of treatment
- Prognosis related to degree and duration of hyperthermia