

The heat is on (and on)

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Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk ...	• • • •

Hyperthermia

Always a challenge
Sometimes life threatening

Expect the unexpected!

Case 1

Woman , 54 years old
2013: severe intoxication quetiapine

Arrival: 11 AM.

8 AM:
120 x 20 mg paroxetine,
Half a liter of brandy

Physical examination

150 kg

RR 150/110; Heart rate 115 bpm

Temp 38,9

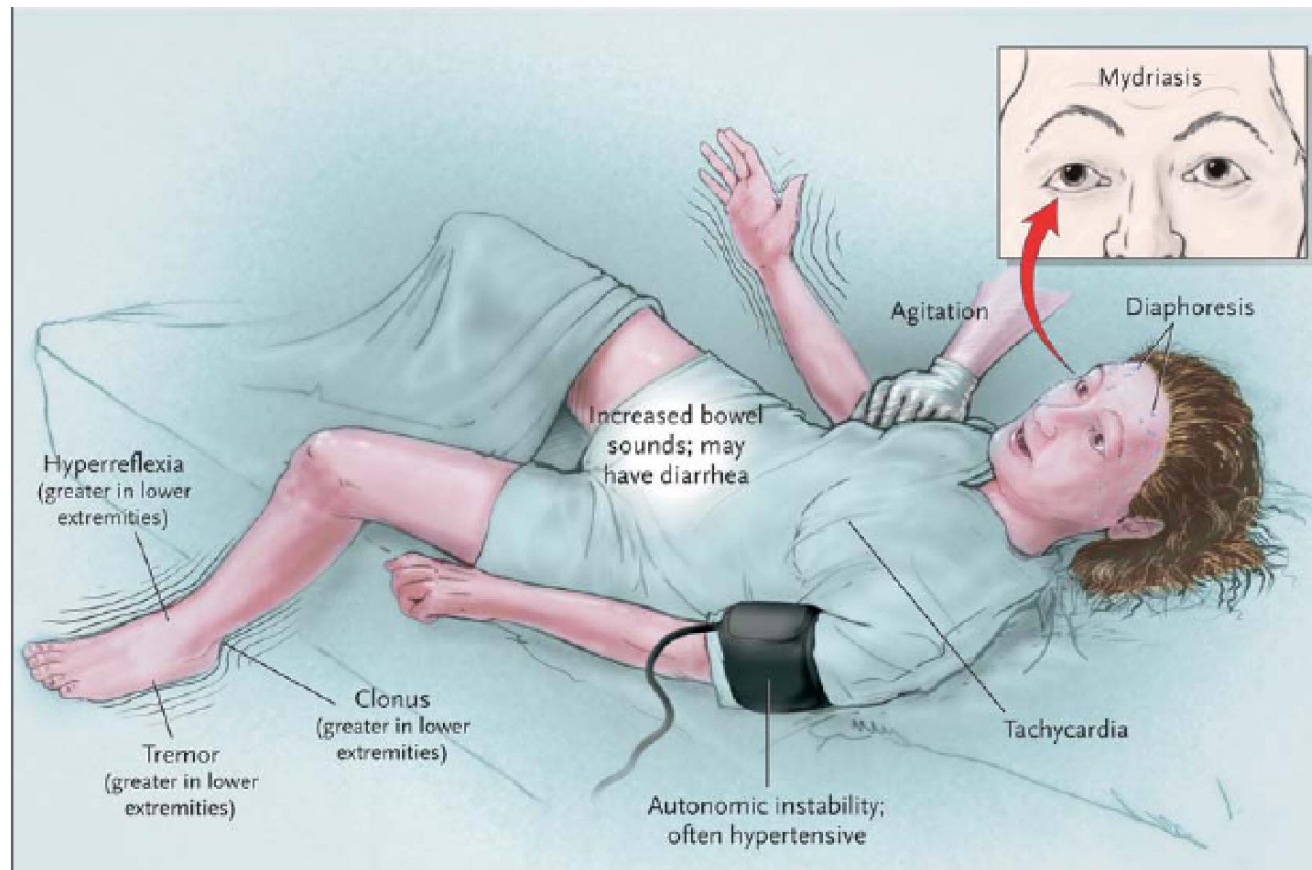
Agitated,

Trembling

Hyperreflexia

CK: 467 U/l

Conclusion: serotonergic syndrome



Tests

Lumbar puncture: normal

Urine culture: E Coli

TSH normal

CT brain: no abnormalities

Blood and other cultures: all negative

Lab: ANA/ds DNA neg. Anti MPO en PR3 neg.

Treatment

Active charcoal

Midazolam,

Paracetamol

Antibiotics (ceftriaxone)

Intubation (propofol) because of ARDS

Cooling (but not very long and aggressive)

Day 5-12: Cyproheptadine

Clinical course

Antibiotic therapy not succesful.

Temperature stays elevated

Develops severe rhabdomyolysis

- Maximum CK 17.000 day 22
- Returns to normal day 30

Paroxetine levels therapeutic at days 13

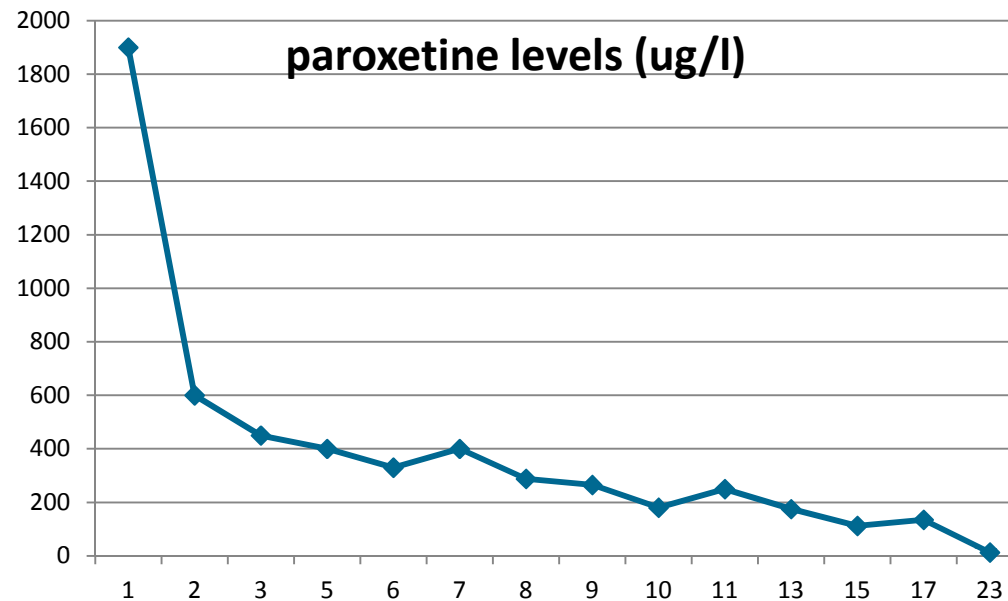
Paroxetine levels undetectable from day 23

Course

Dag	Paroxetinespiegel	CK	temp	HF	opm
01-10-2014	>1900	467	37.6	120	Actief kool, midazolam, ceftriaxon
02-10-2014	600	1116	40.3	140	Intubatie, propofol
03-10-2014	450	1369	39.9	100	
04-10-2014					Genta toegevoegd
05-10-2014	400	814	41.1	130	
06-10-2014	330	1614	39.2	100	Cyproheptadine 12mg oplaad, daarna 4dd8mg
07-10-2014	400	1507	39.5	110	
08-10-2014	288	1773	39.9	120	
09-10-2014	265	2694	39.0	100	Eenmalig vanco
10-10-2014	180	2159	38.7	100	
11-10-2014	250	1046	39.5	105	
13-10-2014	175	408	39.8	110	
15-10-2014	112		39.5	100	
16-10-2014		524	40.0	120	
17-10-2014	135		41.7	130	Koelen
18-10-2014		1722	39.3	120	Co-trimoxazol start. Clonidine start (stop 19-10)
19-10-2014		1571	37.4	100	Cyproheptadine gestopt. Start erytromycine. Start CVVH
20-10-2014		8603	38.2	100	
21-10-2014		9516	37.9	105	
22-10-2014		11405	40.5	135	
23-10-2014	13	17625	38.4	105	
24-10-2014		15984	38.0	100	Sedatie gestaakt
25-10-2014		8916	38.7	100	Dantroleen gestart (1dag)
26-10-2014		5022	39.4	105	
27-10-2014		2884			

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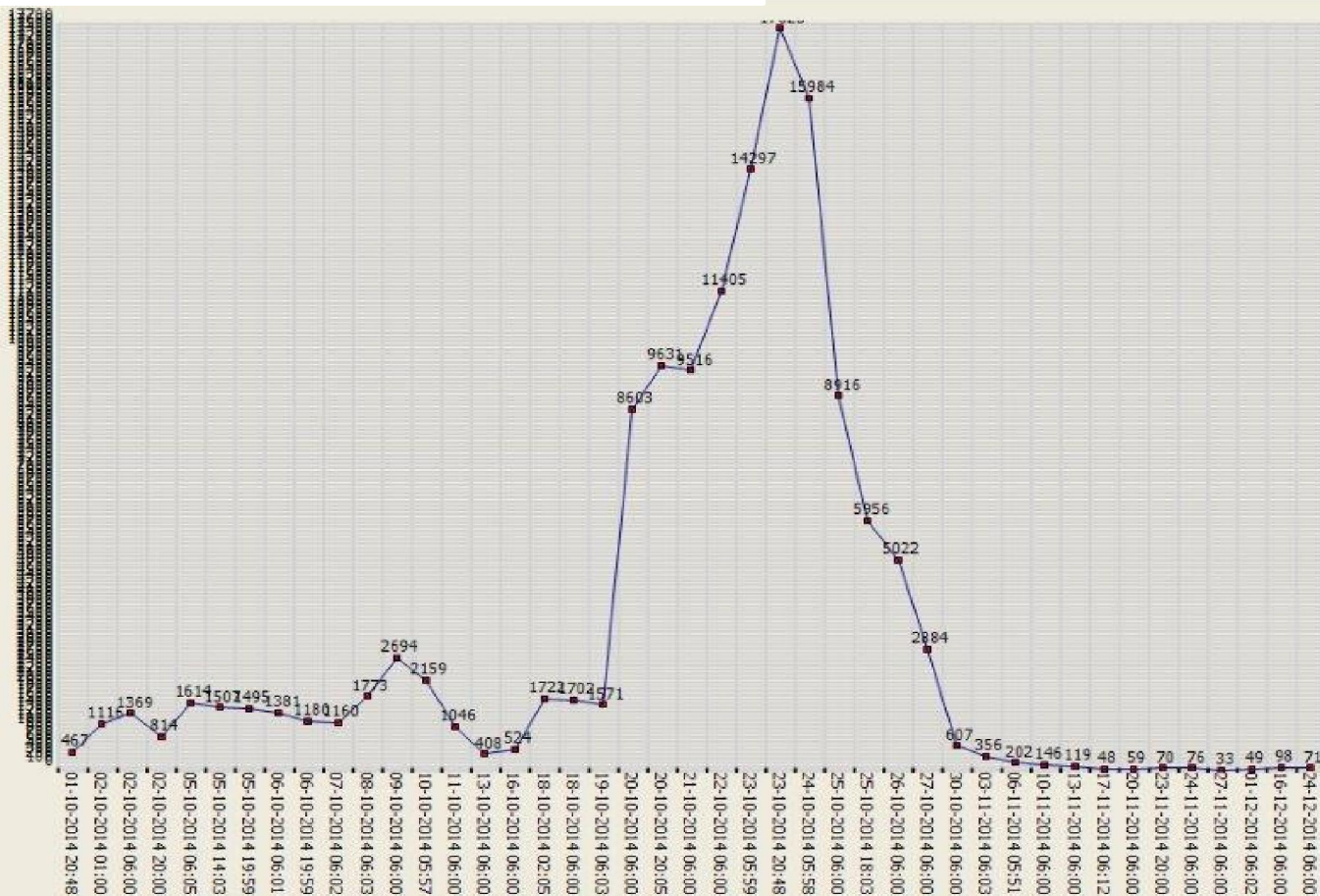


Half life 24 hours

Saturating kinetics

Inhibits own metabolizing route (CYP2D6)

This patient 150 kg!



☐ CK

Paroxetine
 therapeutic
 very low

Clinical course

Many complications

Day 87 the patient dies

Respiratory insufficient

Still hyperthermia

No rhabdomyolysis anymore

Summary

Fatal paroxetine intoxication

Prolonged paroxetine exposure (2-3 weeks)

Long term rhabdomyolysis (5-6 weeks)

Persistent hyperthermia (13 weeks)

Serotonin syndrome and neuroleptic malignant syndrome: Distinguishing features

	Serotonin syndrome (SS)	Neuroleptic malignant syndrome (NMS)
Onset	Within 24 hours	Days to weeks
Neuromuscular findings	Hyperreactivity (tremor, clonus, reflexes)	Bradyreflexia, severe muscular rigidity
Causative agents	Serotonin agonist	Dopamine antagonist
Treatment agents	Benzodiazepine, cyproheptadine	Bromocriptine
Resolution	Within 24 hours	Days to weeks

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Case 2

Woman, 20 years

Possible 2,4-dinitrophenol (**DNP**) – intoxication

Eating disorder, used many diet- and energy products (e.g. Meridia, Guarana).

Medication: Diazepam en Fluoxetine

Admits using DNP on a daily base

Increased dose because of upcoming birthday and wish to lose more weight.

Complaints: dyspnoea, nausea, perspiration,
muscle aches in arms and legs

Primary survey

- A: Airway free
- B: Breathing 40/min, sat 99% without oxygen,
- C: Pulse 140bpm (ECG: ST), RR 170/70mmHg,
- D: Max EMV, normoglycaemia
- E: Temperature rapidly rising (in 30 minutes
T37.4°C to 38.5°C), painful extremities on
touching

Lab on arrival:

ABG: pH 7.49 / pO₂ 11.8kPa / pCO₂ 3.8kPa / bic
20.9mmol/L / BE-1.1

ASAT 463U/L, ALAT 136U/L, LDH 1925U/L

CK 18170U/L

Tox-screen:

Diazepam, Paracetamol en Fluoxetine: therapeutic

Cannabis: positive

Amphetamine / Barbiturate/ Cocaine / Methadone /
Opiates / TCA: negative

DNP

1933: Introduction for weight reduction

1938: FDA ban because of side effects

Until 2001 hardly severe intoxications,
increased abuse because of internet sales

2003: Again FDA ban

<http://news.sky.com/story/1477691/interpol-warns-over-potentially-deadly-diet-pills>

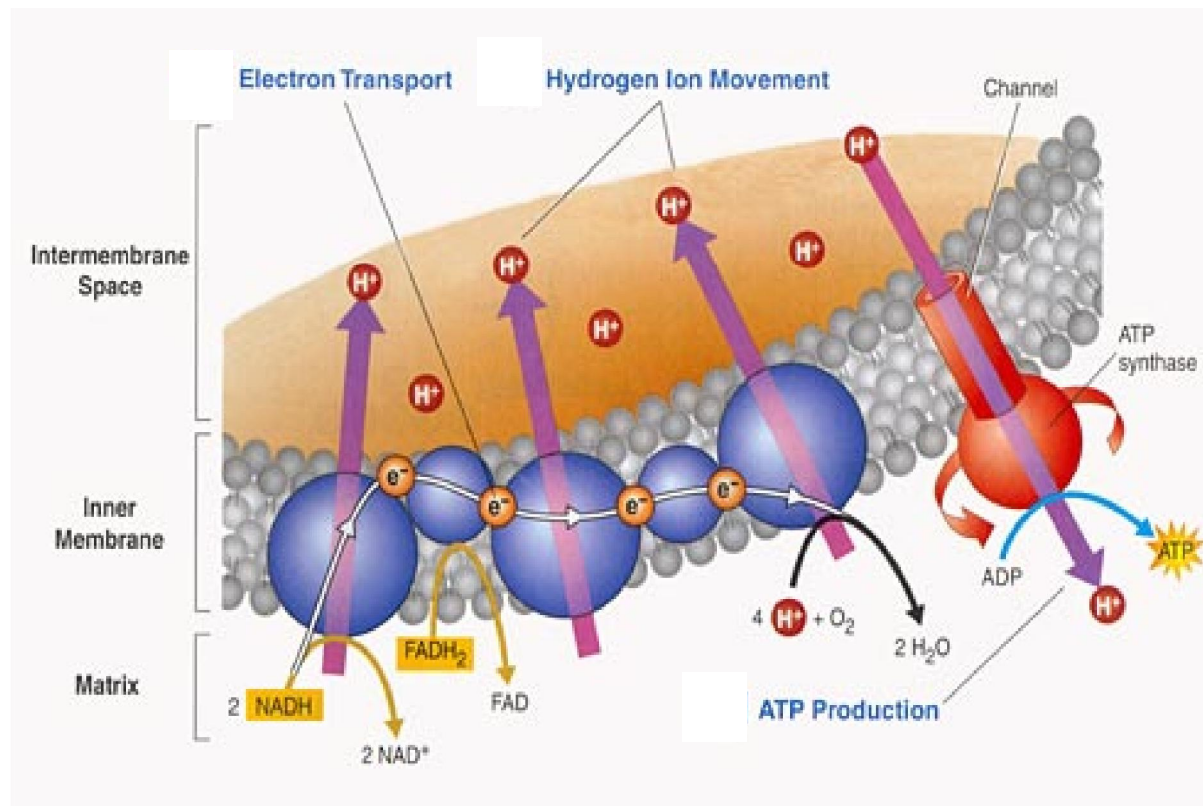
Who are at risk?

- A. Young people with eating disorders
- B. Bodybuilders
- C. People working in agriculture industry



Mechanism of action

Uncouples oxidative phosphorylation in mitochondria



Cell switches to burning of fat

Toxic dose

1-3 mg/kg toxic within a few hours

Median time to death: 14 hours

One single dose of 1-3 g fatal in adults,
3 g fatal if taken in a period of 5 days

Inhalation or dermal exposure systemically toxic

Kinetics

- Absorption: fast
- V_d : ?
- Protein binding: probably high (?)
- Elimination: excretion via kidney, no accumulation
- Half life: estimated 5-14 days

Differential

- Intoxication drugs of abuse (cocaine, amphetamin)
- Intoxication with other diet products
- Thyreotoxic crise
- Sepsis

Therapy

General

- Start aggressive treatment directly
- Beware of difficult intubation because of muscle hypertonicity

Absorption reduction

- Active charcoal
- Gastric lavage ??

Therapy

Symptoms

- Cool the patient!
- In agitated patients: benzodiazepines
- Dantrolene possibly useful
- Intravenous glucose
- If seizures: diazepam iv
- No Haloperidol

In summary

The heat goes on (and on)

In neuroleptic malignant syndrome
This paroxetine intoxication?

DNP

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