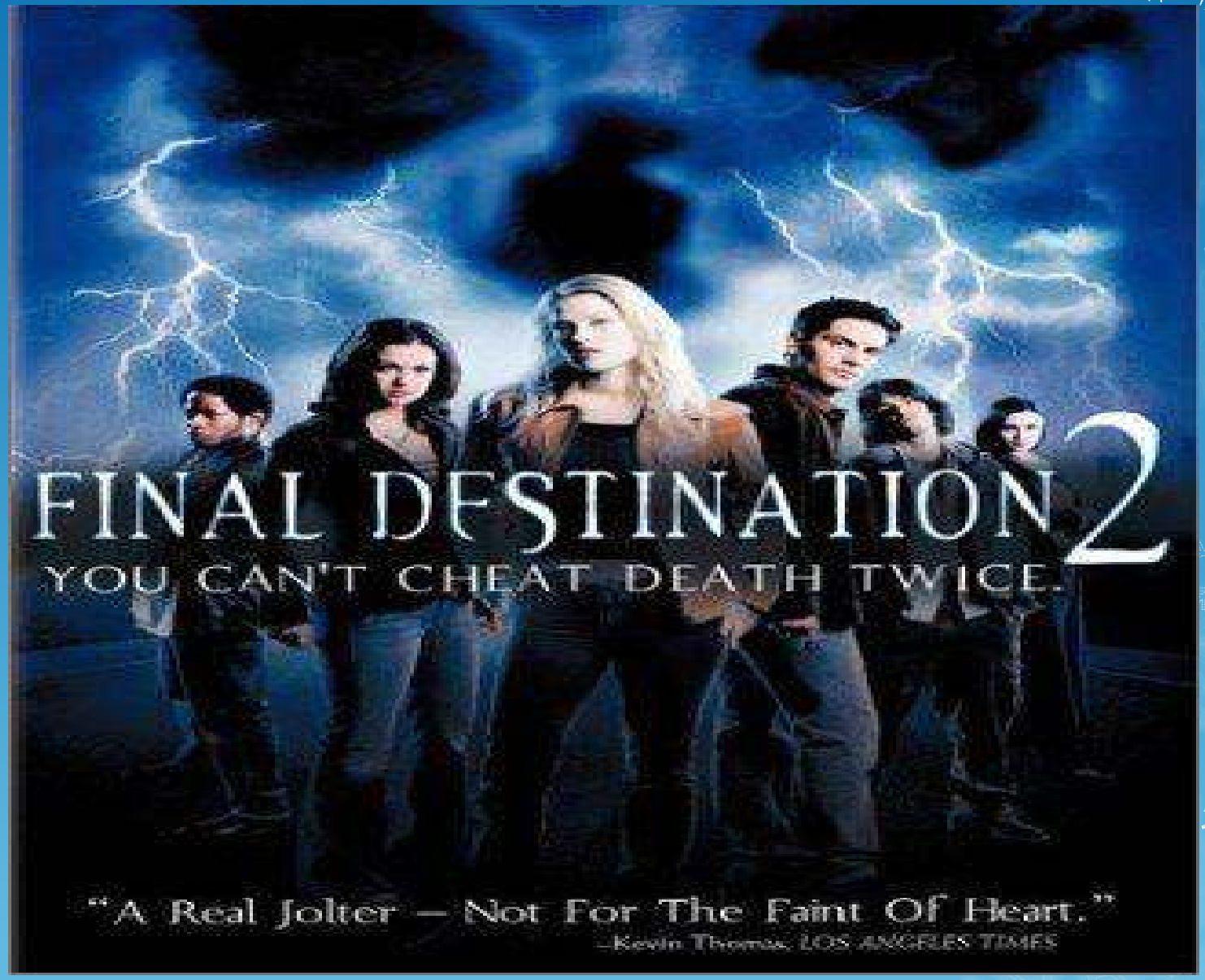
Inter-Hospital Grand Round

Dr CH Ng, MO, ICU, KWH

19/11/2013


FINAL DESTINATION 2
YOU CAN'T CHEAT DEATH TWICE.
"A Real Jolter — Not For The Faint Of Heart."
–Kevin Thomas, LOS ANGELES TIMES

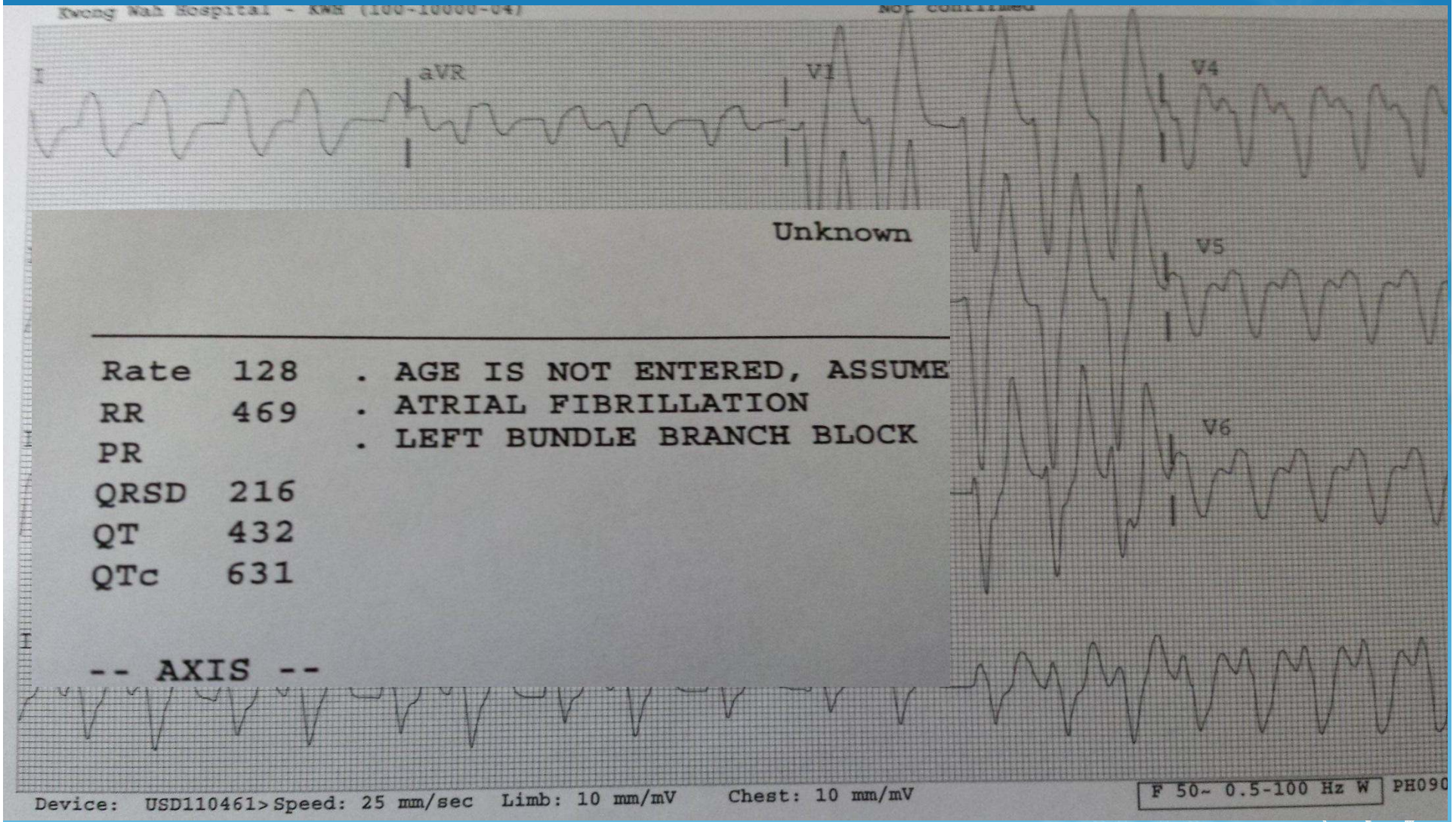
Case One

- **Case one**
- 19/F
- GBS with complete recovery
- Migraine/headache with normal CT brain; MRI brain/spine in 03/2010 : tiny non-specific hyperintense focus of unknown significance in the subcortical region of left frontal lobe
- ? Obesity, on ? self-purchased slimming agent 'Yanhee' from the internet
- Depression, on medication since 2009
- Last admission in 03/2012 because of DO

Case One

- Noted generalised limb twitching by her mother on 07/06/2013 at ~1130pm
- The convulsion transiently aborted by Valium in AED
- ECG showed cardiac arrhythmia

Case One


aVR
V1
V4
V5
V6
Unknown
Rate 128
RR 469
PR
QRSD 216
QT 432
QTc 631
. AGE IS NOT ENTERED, ASSUME
. ATRIAL FIBRILLATION
. LEFT BUNDLE BRANCH BLOCK
-- AXIS --
Device: USD110461>Speed: 25 mm/sec Limb: 10 mm/mV Chest: 10 mm/mV
F 50~ 0.5-100 Hz W

Case Presentations

- ECG: widened QRS complexes with prolonged QTc
- Developed into VT with hypotension, with cardioversions done in AED and in ward
- To ICU
- Hong Kong poison information centre was contacted and provided some suggestions

Case One

- **What is the diagnosis and any suggested management?**

Drug Overdose ? TCA poisoning ?

NaHCO3 given for alkalisation

Case One

Table 1

Risk Factors

Age
Female gender
Bradycardia
Left ventricular failure
Recent cardioversion
Congenital long QT sync
Electrolyte abnormalities
Hypomagnesemia
Hypokalemia
Hypocalcemia
Hepatic dysfunction

Source: References 2, 3.

Table 2

Drugs Associated with QT Prolongation and TdP

Antiarrhythmics	Antimicrobials	Antidepr
Amiodarone	Levofloxacin	Amitript
Sotalol	Ciprofloxacin	Desipran
Quinidine	Gatifloxacin	Imipram
Procainamide	Moxifloxacin	Doxepin
Dofetilide	Clarithromycin	Fluoxetir
Ibutilide	Erythromycin	Sertralin
	Ketoconazole	Venlafax
	Itraconazole	

Source: References 1, 3, 4, 8, 9, 14.

Table 3

Drug Interactions That May Delay Repolarization

Isozyme	Drug Shown to Prolong QT	Inhibitor
CYP3A4	Amiodarone Erythromycin Quinidine Haloperidol Pimozide Tacrolimus Cisapride Dofetilide Disopyramide Tamoxifen Mesoridazine	Cimetidine Erythromycin Indinavir Ketoconazole Ritonavir Diltiazem Clarithromycin Itraconazole
CYP1A2	Imipramine	Cimetidine Fluvoxamine Ciprofloxacin
CYP2D6	Thioridazine Imipramine Amitryptyline Flecainide Doxepin Tamoxifen	Amiodarone Diphenhydramine Chlorpheniramine Quinidine Fluoxetine

Source: References 1, 3, 13.

Case One

- Refractory generalised convulsion, later controlled by Dilantin, Dormicum infusion and Propofol infusion
- Cardiac rhythm converted back to sinus rhythm
- Urgent CT brain (plain): NAD
- Still metabolic acidosis with worsening BE, with repeated doses of $NaHCO_3$ given
- **Generalised muscle rigidity** with **provocable lower limb clonus**
- **Serum CK level >10000**
- **Hyperthermia**, put on external passive cooling

Case One

- What happened to the patient then and any suggested diagnosis?

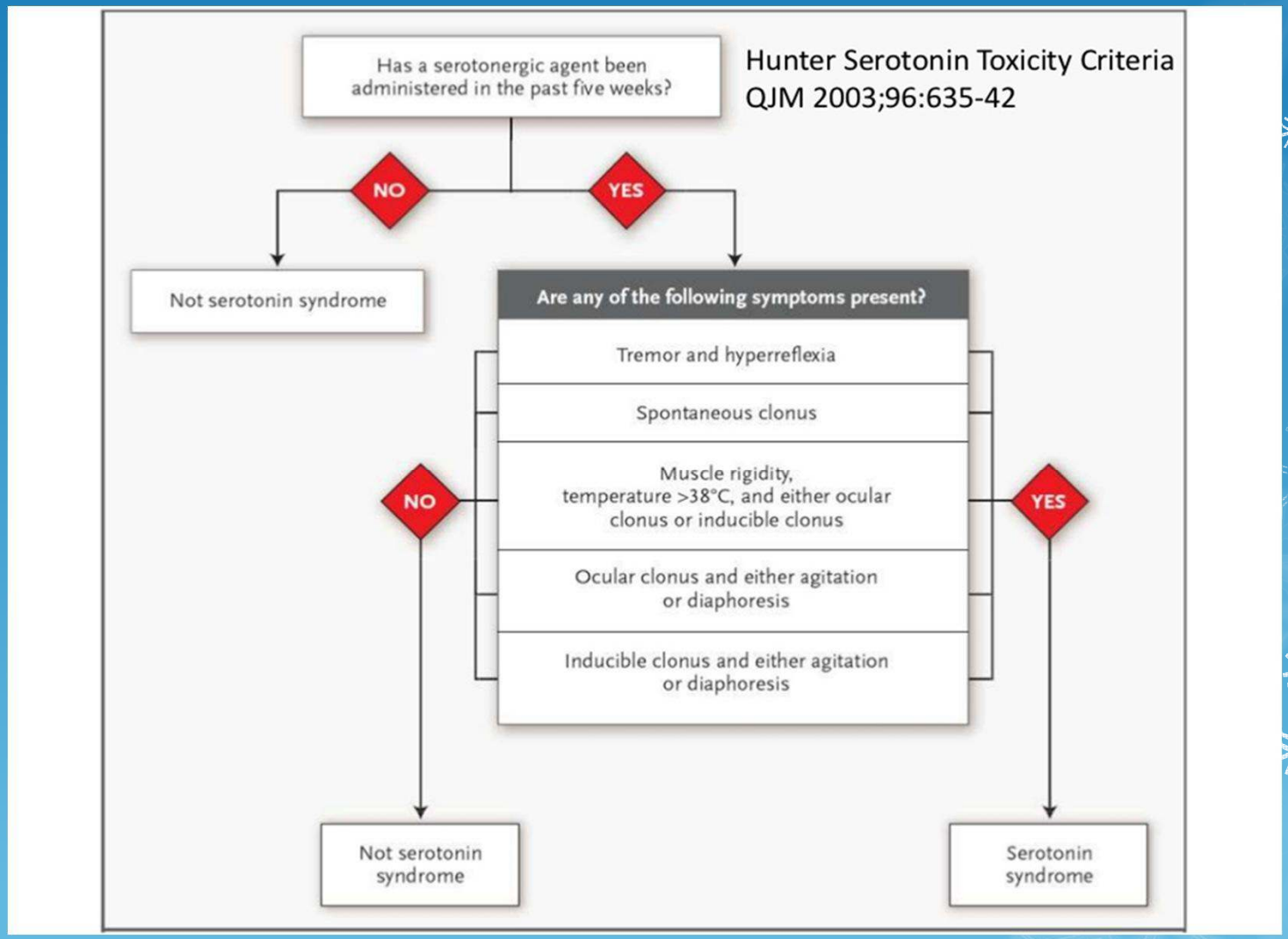
Case One

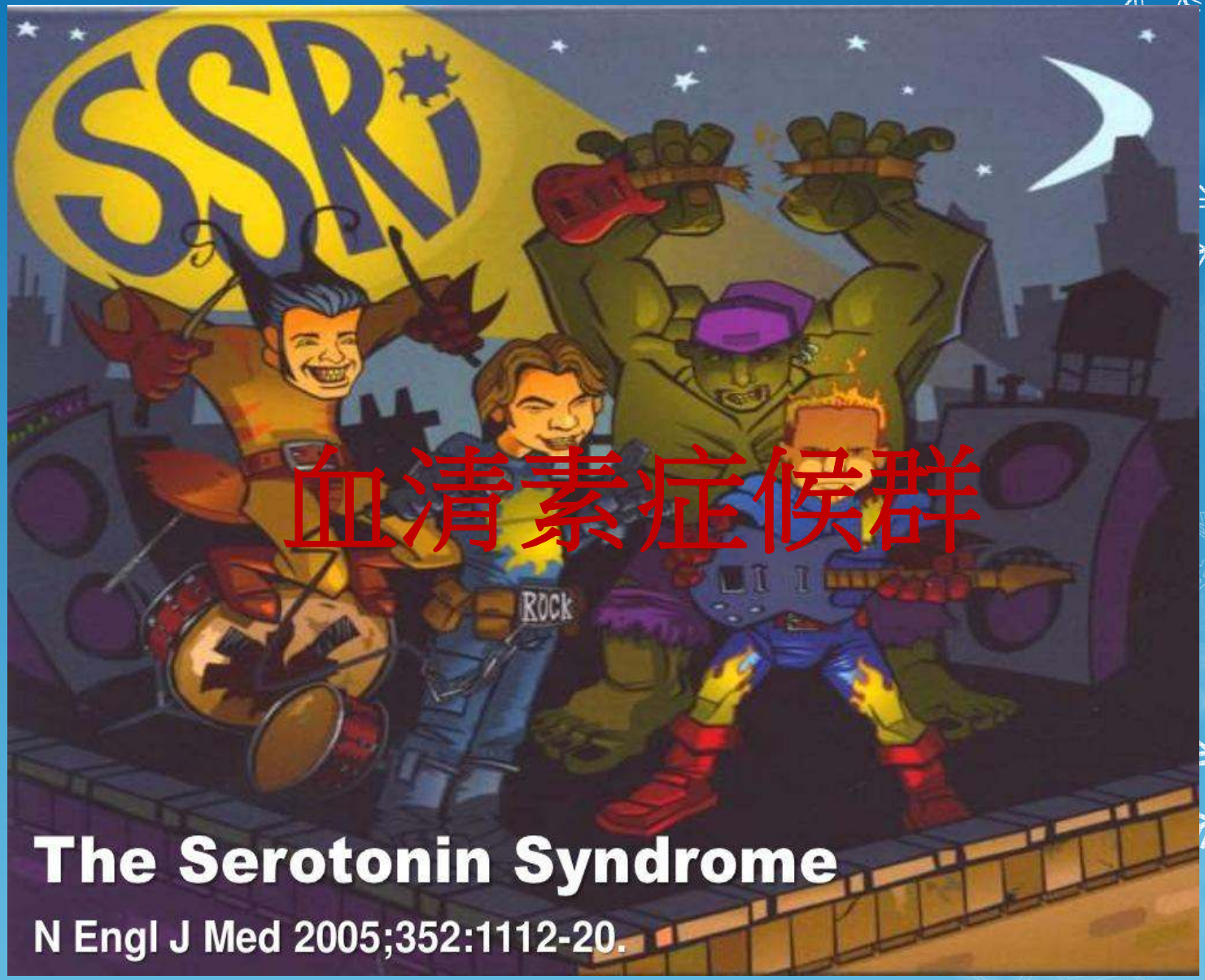
- Hx:

Serotonin Syndrome?

- P/E + Ix:
  - Generalised muscle rigidity with provocable lower limb clonus
  - Serum CK level > 10000
  - Hyperthemia

Case One


Has a serotonergic agent been administered in the past five weeks?
Hunter Serotonin Toxicity Criteria
QJM 2003;96:635-42
NO
YES
Not serotonin syndrome
Are any of the following symptoms present?
Tremor and hyperreflexia
Spontaneous clonus
Muscle rigidity, temperature >38°C, and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis
NO
YES
Not serotonin syndrome
Serotonin syndrome


SSRI
ROCK
The Serotonin Syndrome
N Engl J Med 2005;352:1112-20.

血清素症候群

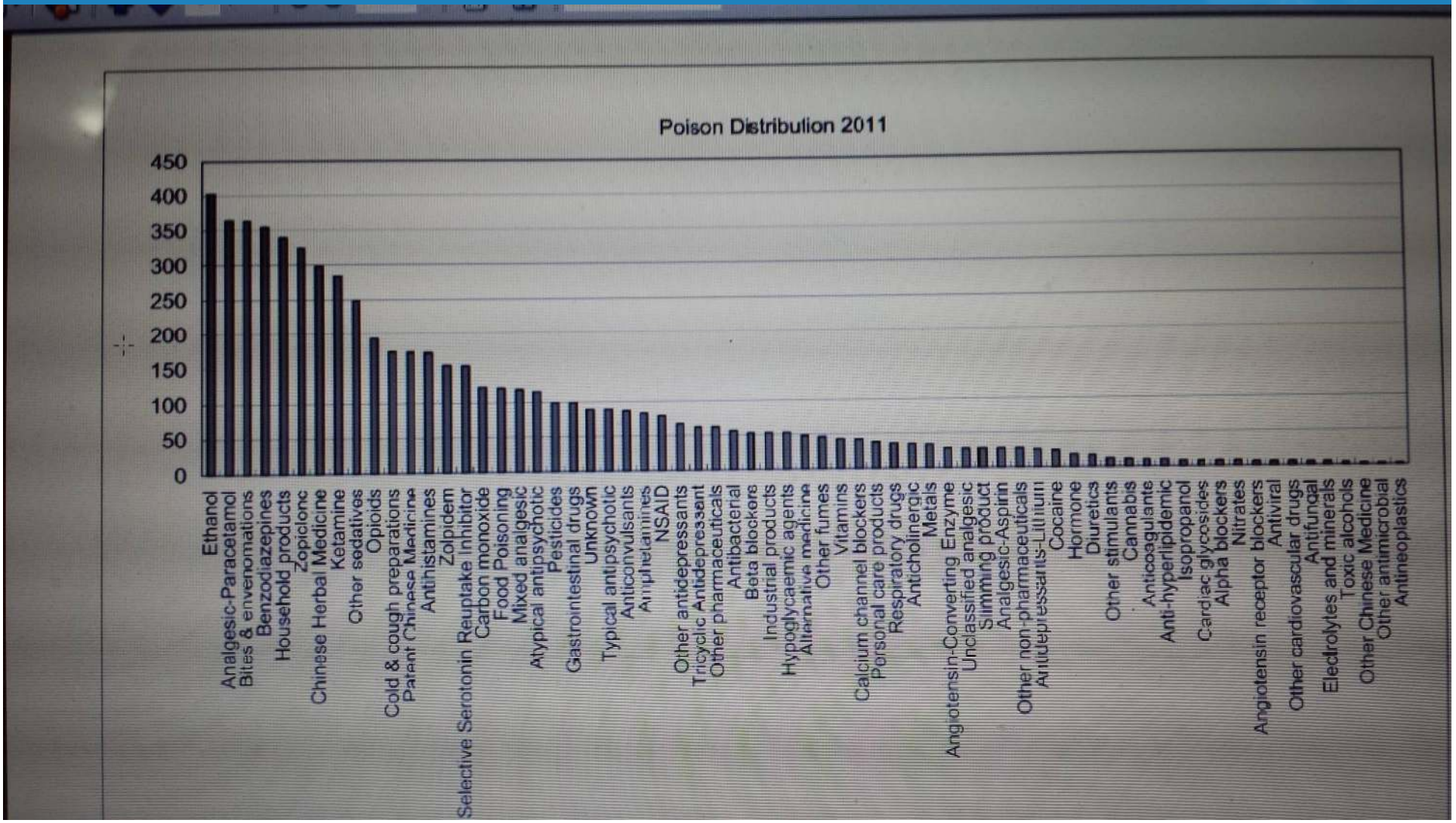
Serotonin Syndrome

- A potentially life-threatening condition associated with increased serotoninergic activity in the CNS
- Seen with therapeutic case, inadvertent interactions between drugs, and intentional self-poisoning
- Affects all age groups
- Under-reported, the incidence is unknown with some prescription-event monitoring indicated an incidence of 0.5-1 per 1000 patient months of treatment with serotoninergic agents
- Increasing incidence mirrors increasing use of serotoninergic agents

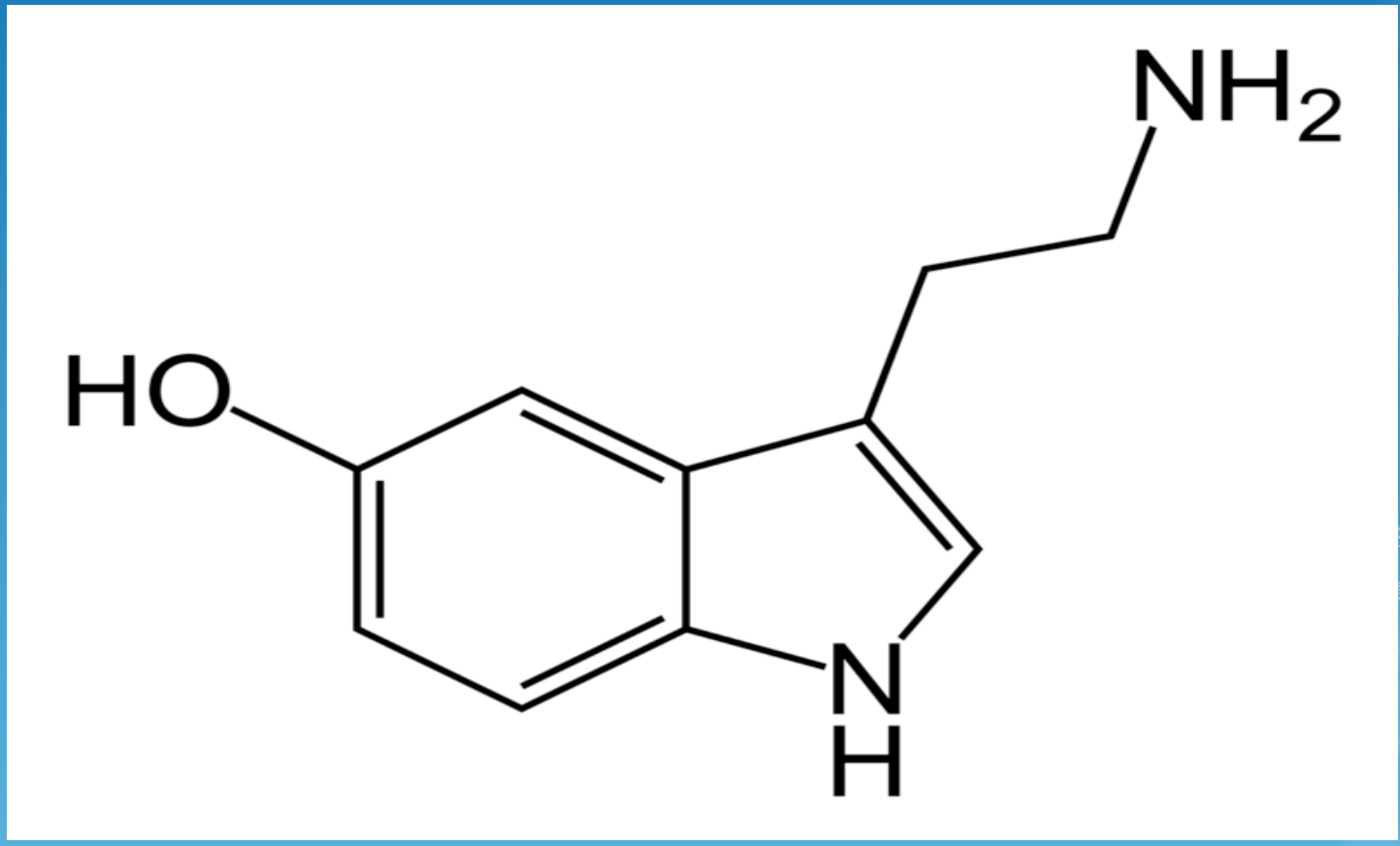
Serotonin Syndrome

- Classically associated with the simultaneous administration of 2 serotoninergic agents
- But can occur after the start of a single agent or increased dosage of a serotoninergic agent in those who are particularly sensitive to serotonin
- Diagnosis made on clinical grounds
- Majority of cases present within 24 hrs, and most within 6 hrs of a change in dose or an initiation of a drug

Serotonin Syndrome

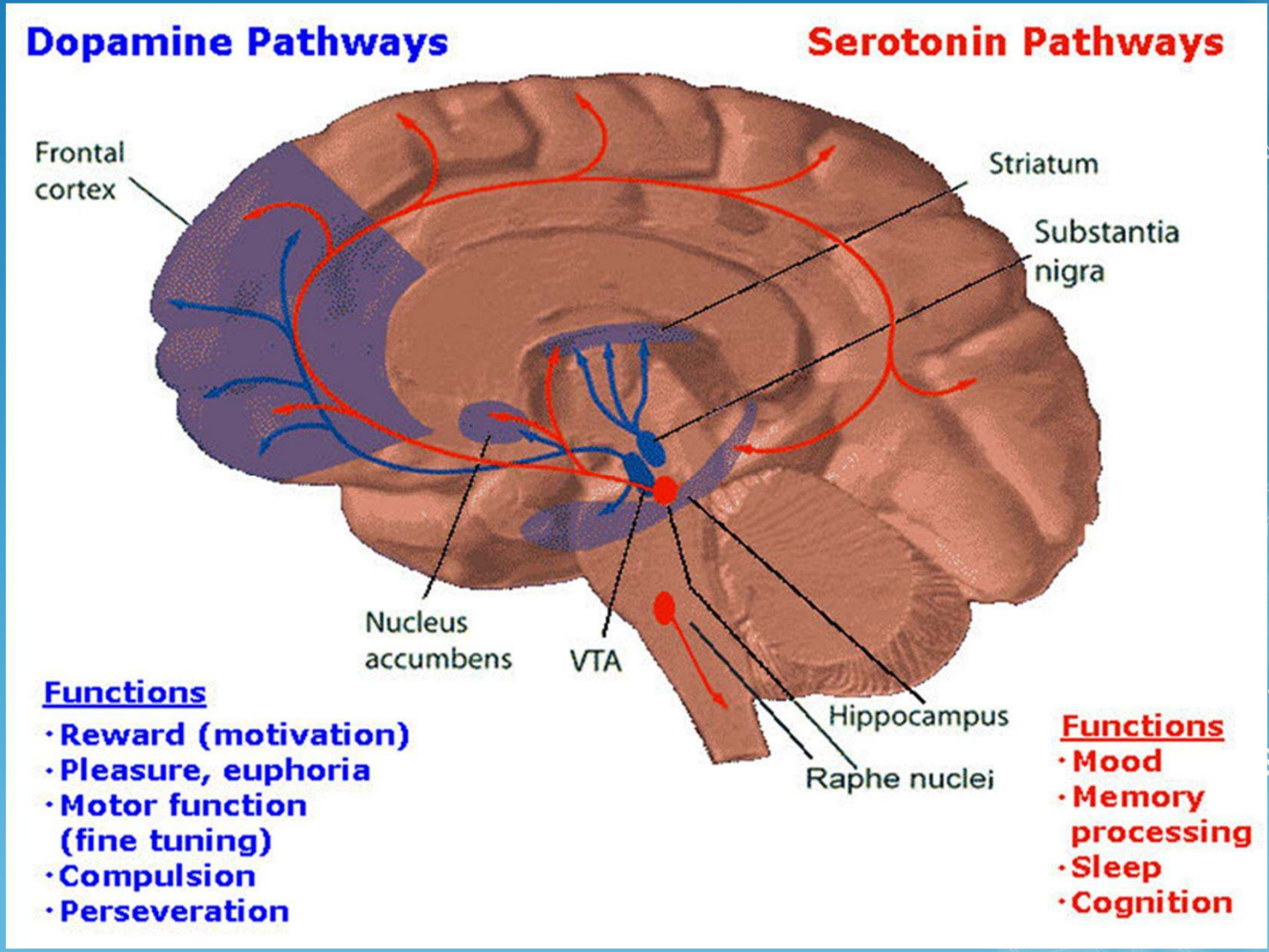


Serotonin Syndrome

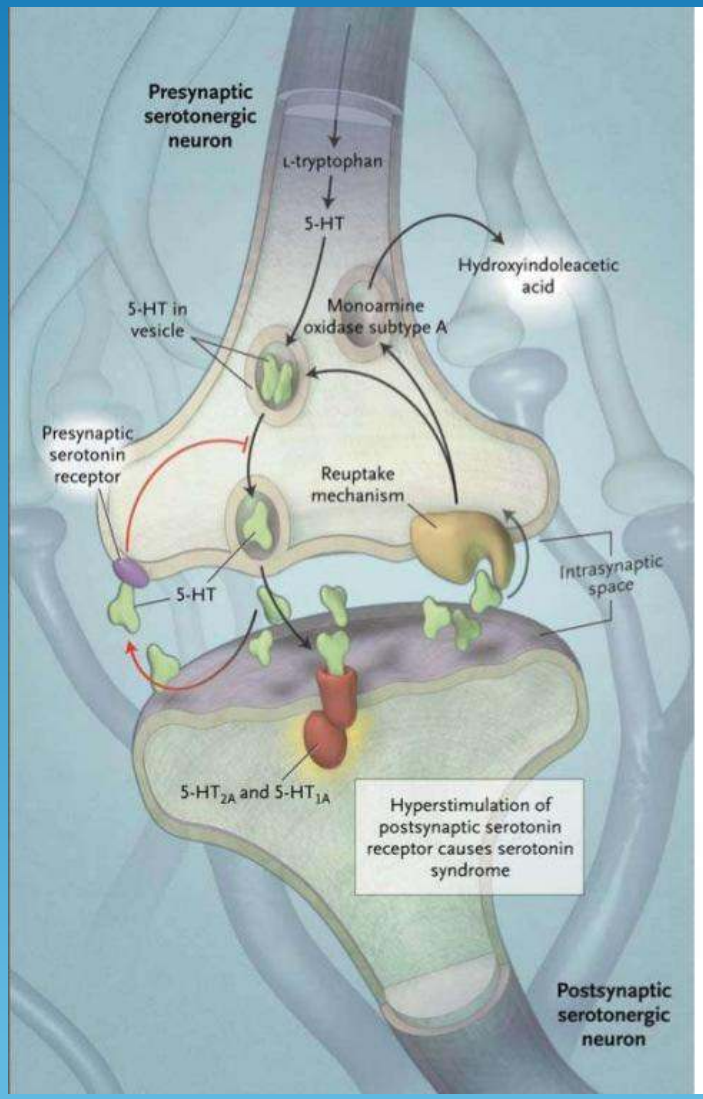


Discovered in 1948

Serotonin Syndrome



Serotonin Syndrome



Serotonin Biosynthesis and Metabolism

Serotonin is produced in presynaptic neurons by hydroxylation and decarboxylation of l-tryptophan. Serotonin is then incorporated into vesicles, where it resides until it is needed for neurotransmission. After axonal stimulation, serotonin is released into the intrasynaptic space; presynaptic serotonin receptors function as a feedback loop to inhibit exocytosis of vesicles (shown in red). Serotonin then binds to postsynaptic receptors to effect neurotransmission. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron, where it is reintroduced into vesicles. Serotonin is then metabolized by monoamine oxidase subtype A to hydroxyindoleacetic acid.

Serotonin Syndrome

- Actions:
  - Excitation/inhibition of CNS neurons
  - Stimulation of peripheral nociceptive nerve endings
  - Vascular effects:
    - Constriction (direct and via sympathetic innervation)
    - Dilatation
    - Platelet aggregation
    - Increased microvascular permeability
  - Increased GI motility:
    - Direct excitation of smooth muscle and indirect action via enteric neurons
  - Contraction of other smooth muscles, e.g. bronchi, uterus

Serotonin Syndrome

- Peripheral roles:
  - Peristalsis
  - Vomiting
  - Platelet aggregation and haemostasis
  - Inflammatory mediator
  - Sensitisation of nociceptors
  - Microvascular control

Serotonin Syndrome

- Central roles:
  - Control of appetite
  - Sleep
  - Mood
  - Hallucination
  - Stereotyped behaviour
  - Pain perception
  - Vomiting

Serotonin Syndrome

- Receptors (5HT-1 to 5HT-7):
  - 5HT-1: anxiolytic and antidepressant
  - Subtypes: 5HT-1A, 5HT-1B, 5HT-1D, 5HT-1E, and 5HT-1F
  - 5HT-2: hallucinogens
  - Subtypes: 5HT-2A, 5HT-2B, and 5HT-2C

Serotonin Syndrome

- History:
  - First described (1959) in a patient with TB who received meperidine along with iproniazid and died of a ‘fatal toxic encephalitis’
  - Oates (1960) suggested excess serotonin as the cause of symptoms after MAOIs with tryptophan
  - Animal work (1980s) attributed MAOI/pethidine interaction to excess serotonin
  - Insel (1982) often quoted as describing the serotonin syndrome
  - Sternbach (1991) developed diagnostic criteria for the serotonin syndrome

Serotonin Syndrome

- Clinical features:
  - A detailed description of prescription drugs, OTCs, illicit substances, and dietary supplements used (Trypophan)
  - Ask about the dose, formulation (e.g. sustained release), and any recent changes in medication

Serotonin Syndrome

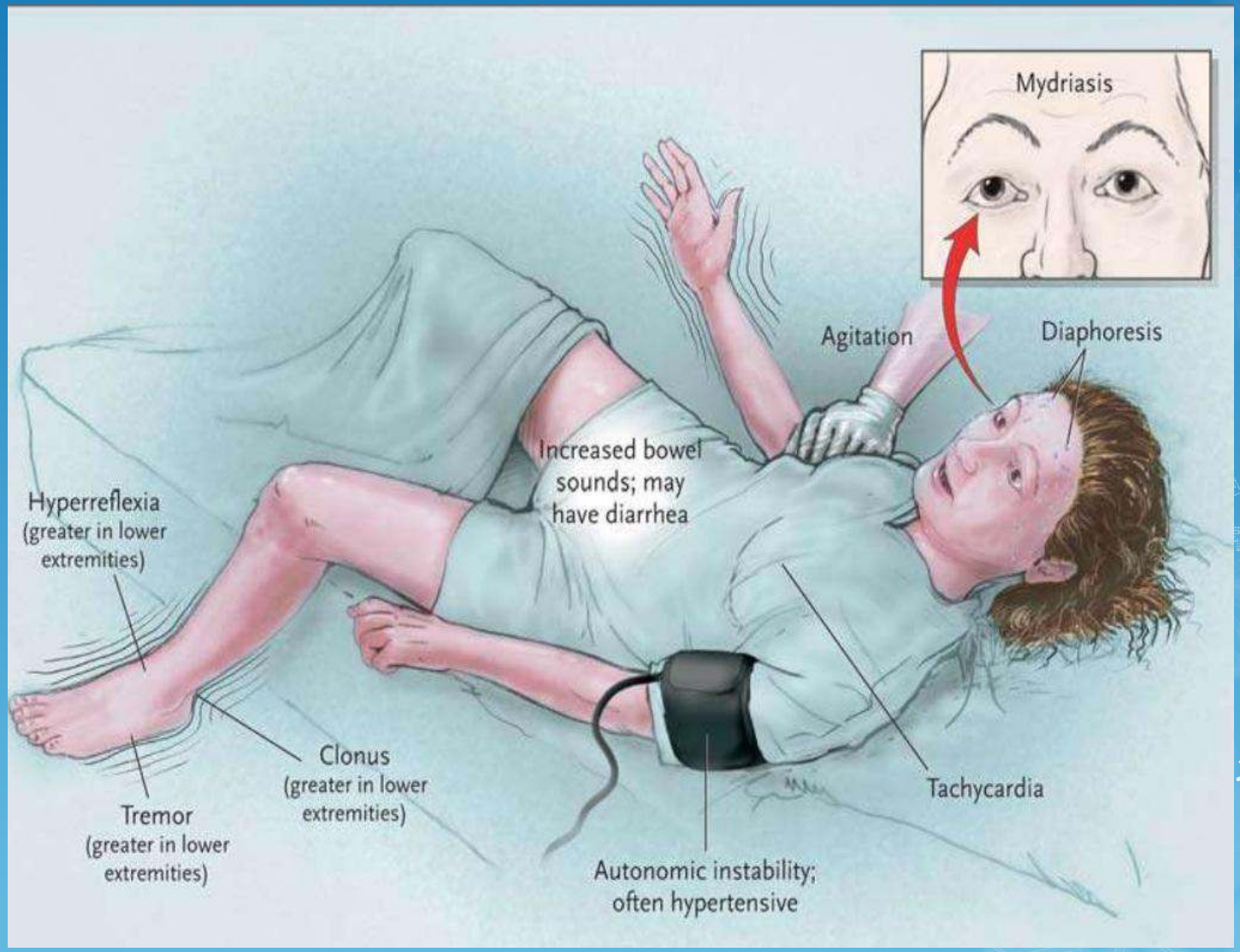
Table 2

Clinical features of serotonin syndrome

Cognitive	Confusion, agitation, hypomania, hyperactivity, restlessness
Autonomic	Hyperthermia, sweating, tachycardia, hypertension, mydriasis, flushing, shivering
Neuromuscular	Clonus (spontaneous/inducible/ocular), hyperreflexia, hypertonia, ataxia, tremor

Hypertonia and clonus are always symmetrical and are often much more dramatic in the lower limbs.

Serotonin Syndrome



Serotonin Syndrome

Drugs Associated with the Serotonin Syndrome

- Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
- Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
- Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
- Anticonvulsants: valproate
- Analgesics: meperidine, fentanyl, tramadol, and pentazocine
- Antiemetic agents: ondansetron, granisetron, and metoclopramide
- Antimigraine drugs: sumatriptan
- Bariatric medications: sibutramine
- Antibiotics: linezolide (a MAOI) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
- Over-the-counter cough and cold remedies: dextromethorphan
- Drugs of abuse: MDMA, or “ecstasy”, LSD, 5-methoxydiisopropyltryptamine (“foxy methoxy”), Syrian rue (contains harmine and harmaline, both MAOI)
- Dietary supplements and herbal products: tryptophan, Hypericum perforatum (St. John’s wort), Panax ginseng (ginseng)
- Other: lithium

Serotonin Syndrome

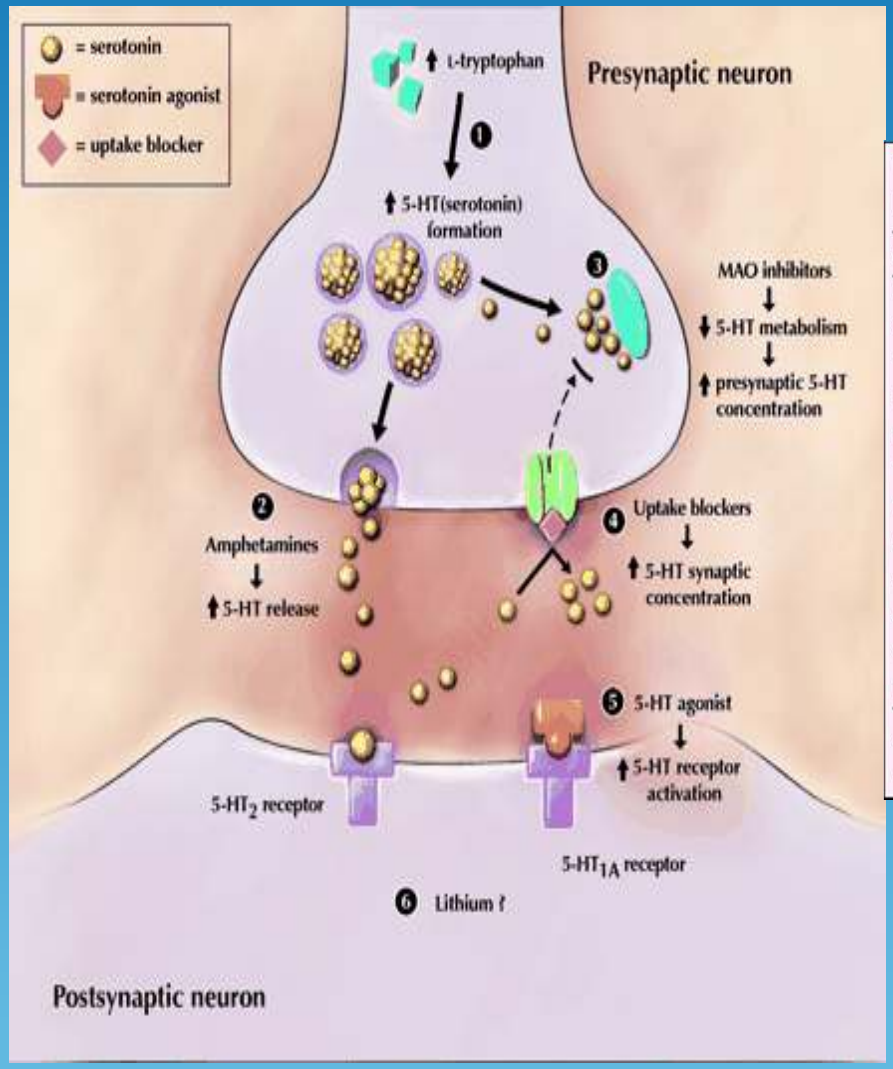


Table 1

Drugs implicated in severe serotonin syndrome*

Drug	*Mechanism*
L-Tryptophan	Serotonin precursor
Selective serotonin reuptake inhibitors	Inhibit serotonin reuptake
Tricyclic antidepressants	Inhibit serotonin reuptake
Monoamine oxidase inhibitors (A>B)	Inhibit metabolism of 5-HT
Pethidine	Serotonin agonist
Tramadol	Inhibits serotonin reuptake
LSD	Partial serotonin agonist
Buspirone	Partial serotonin agonist
Amphetamines and anorectics	↑5-HT release & ↓reuptake
Atypical antidepressants	Various
St John's wort	All of the above?
Lithium	Unknown

* Note: Interactions are more severe between drugs with different mechanisms of increasing serotonin.

Serotonin Syndrome

TABLE.
Diagnostic Criteria for Serotonin Syndrome as Proposed by Birmes and colleagues[22]

	Major Symptoms	*Minor Symptoms*
Mental symptoms	Coma/semi-coma Confusion Elevated mood	Agitation Insomnia Nervousness
Autonomic symptoms	Fever Hyperhidrosis	Blood pressure changes Diarrhea Tachycardia Tachypnea/ dyspnea
Neurological symptoms	Chills Hyperreflexia Myoclonus Rigidity Tremors	Akathisia Impaired coordination Mydriasis

Huska MT, Catalano G, Catalano MC. *CNS Spectr.* Vol 12, No 4. 2007.

Serotonin Syndrome

Box 1: Revised diagnostic criteria for serotonin syndrome[3,9]*

1. Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms plus 2 minor ones

Mental (cognitive and behavioural) symptoms

Major symptoms: confusion, elevated mood, coma or semicoma

Minor symptoms: agitation and nervousness, insomnia

Autonomic symptoms

Major symptoms: fever, hyperhidrosis

Minor symptoms: tachycardia, tachypnea and dyspnea, diarrhea, low or high blood pressure

Neurological symptoms

Major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia

Minor symptoms: impaired co-ordination, mydriasis, akathisia

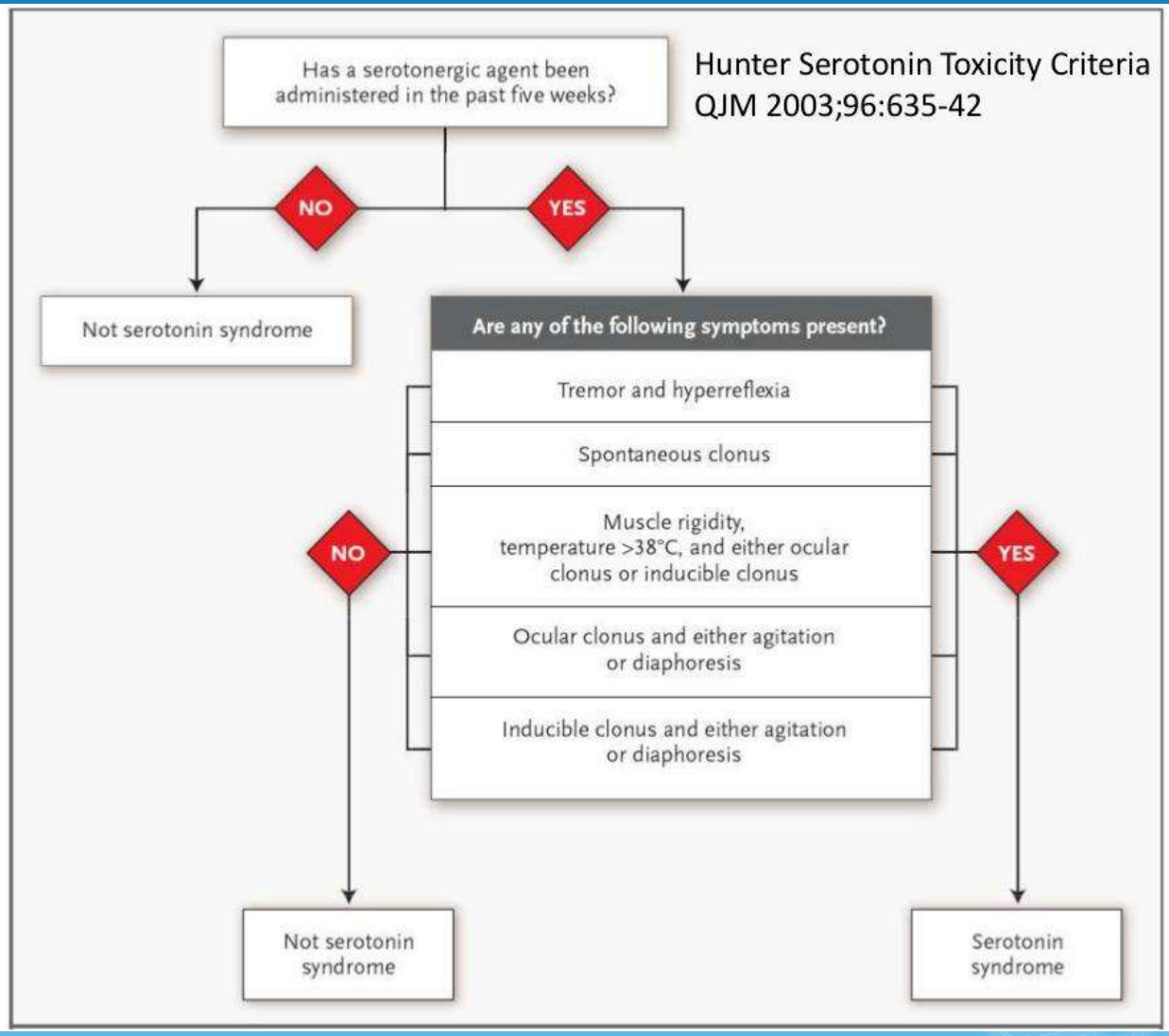
2. These symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotonergic agent.

3. Infectious, metabolic, endocrine or toxic causes must be excluded.

4. A neuroleptic treatment must not have been introduced, nor its dose increased, before the symptoms appeared.

*Adapted from Radomski et al[9]

Serotonin Syndrome



Serotonin Syndrome

- Deemed to be most accurate (84% sensitive and 97% specific when compared with the gold standard of diagnosis by a medical toxicologist)

- In a comparison with the original Sternbach Criteria, the Hunter Criteria performed with greater accuracy and was less likely to miss early, mild, or subacute form of serotonin syndrome

Serotonin Syndrome

Box 2: Major differential diagnoses[2,3]

Malignant neuroleptic syndrome

Infectious causes

Herpetic encephalopathy

Heat stroke

Myocardial necrosis

Delirium tremens

Intoxication by adrenergic or anticholinergic agents

Serotonin Syndrome

Condition	Serotonin syndrome	Anticholinergic "toxidrome"	NMS	Malignant hyperthermia
Medication History	Proserotonergic drug	Anticholinergic agent	Dopamine antagonist	Inhalational anesthesia
Onset	<12 hr	<12 hr	1–3 days	30 min to 24 hr
Vital Signs	Hypertension, tachycardia, tachypnea, Hyperthermia (>41.1°C)	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically < 38.8°C)	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as (46.0°C)
Pupils	Mydriasis	Mydriasis	Normal	Normal
Mucosa	Sialorrhea	Dry	Sialorrhea	Normal
Skin	Diaphoresis	Erythema, hot and dry	Pallor, diaphoresis	Mottled, diaphoresis
Bowel Sounds	Hyperactive	Decreased or absent	Normal or decreased	Decreased
Neuromuscular Tone	Increased, predominantly in lower extremities	Normal	"Lead-pipe" rigidity present in all muscle groups	Rigor mortis–like rigidity
Reflexes	Hyperreflexia, clonus	Normal	Bradyreflexia	Hyporeflexia
Mental Status	Agitation, coma	Agitated delirium	Stupor, alert Mutism, coma	Agitation

Serotonin Syndrome

- Investigations:
  - Serum concentrations do not correlate with clinical features
  - No single test can confirm the diagnosis

CBC
LFT/RFT
CK
Clotting profile
Blood culture
Urinalysis and urine culture
CXR
CT brain; LP and CSF analysis

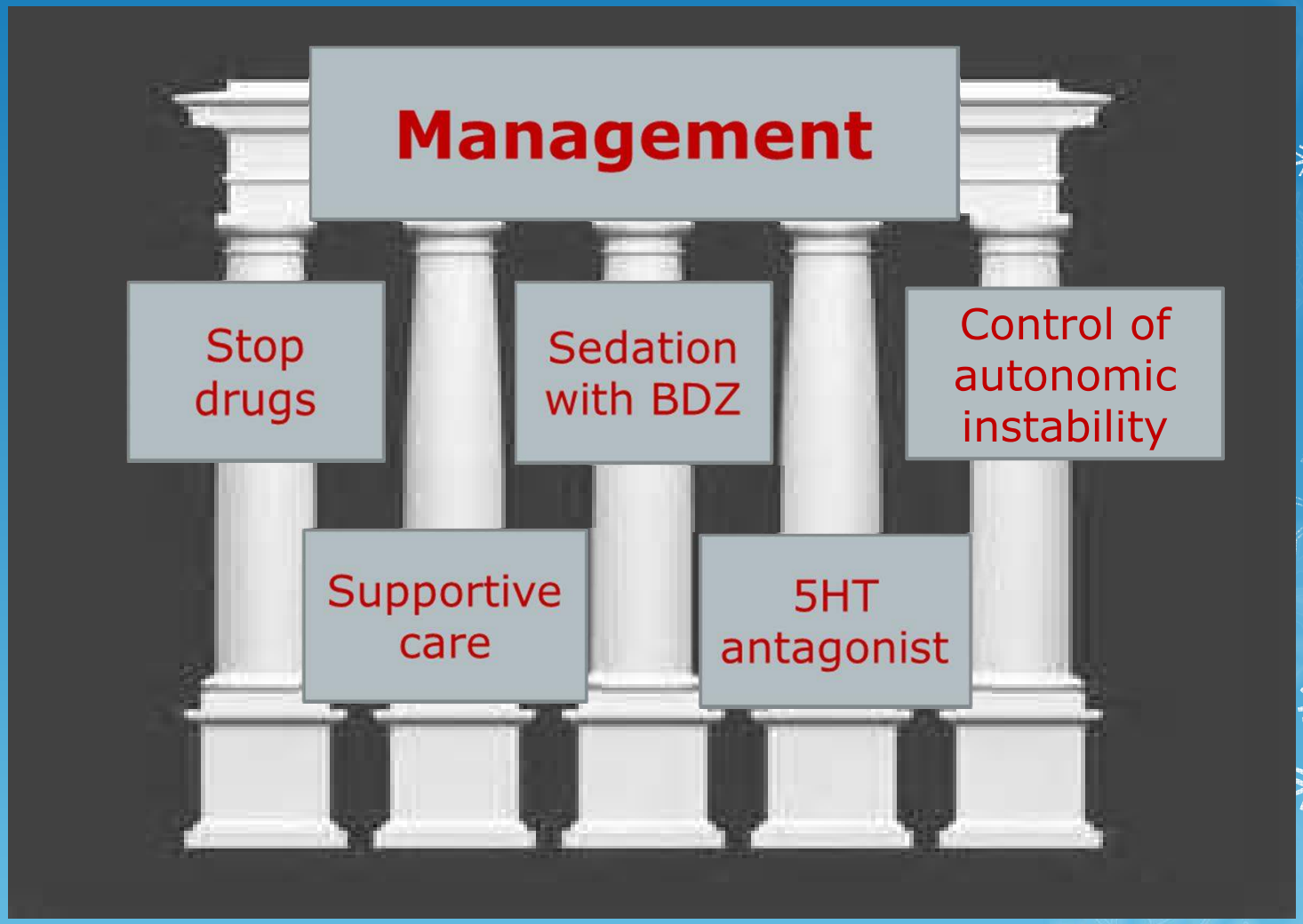
  - In an intentionally overdosed patient, acetaminophen and salicylate concentration should be measured, and an ECG done for signs of toxicity from other agents

Serotonin Syndrome

- Complications:

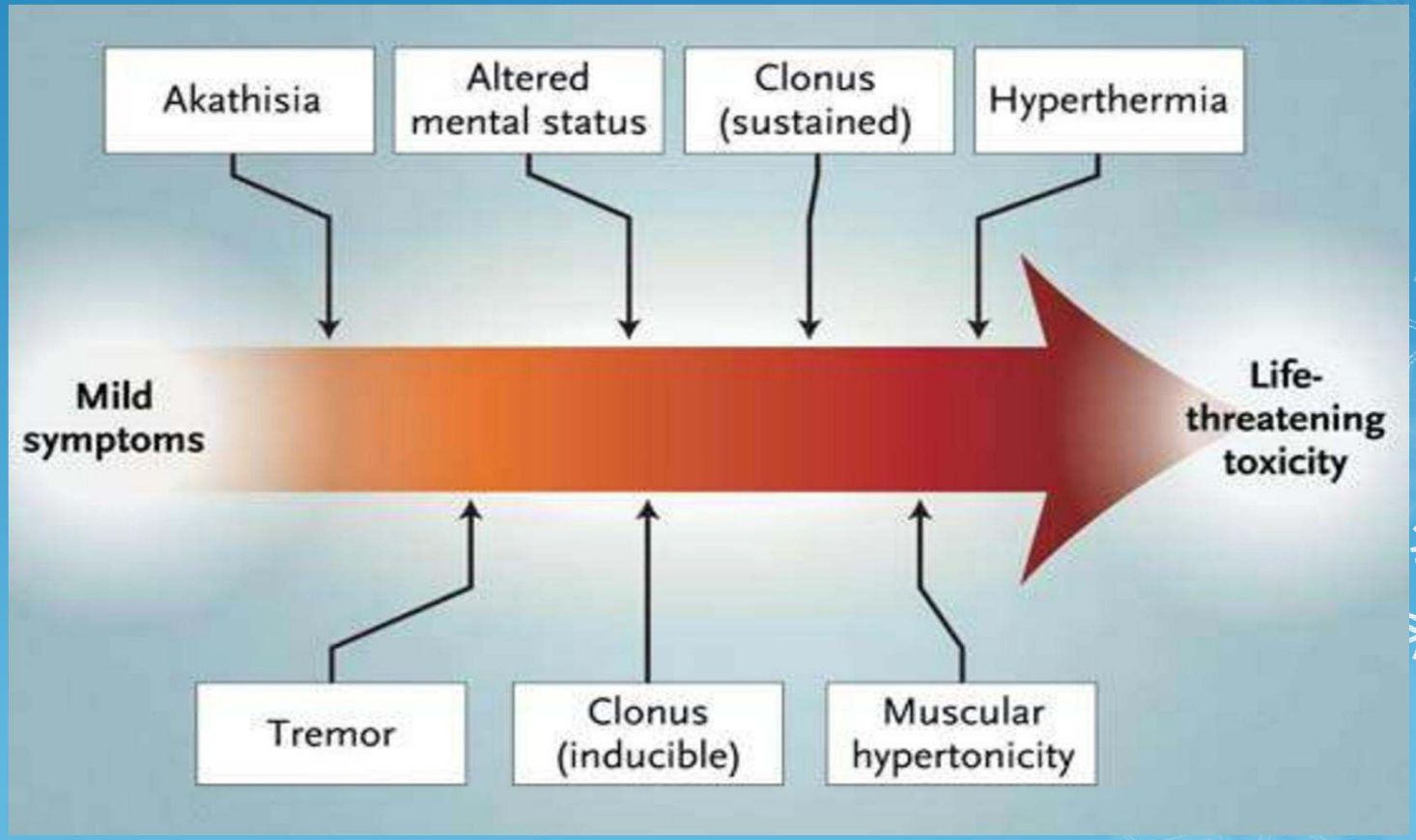
DIC
Rhabdomyolysis
Metabolic acidosis
Renal failure
Myoglobinuria
ARDS

Serotonin Syndrome



Serotonin Syndrome

- Application of these principles varies with the severity of serotonin syndrome



Serotonin Syndrome

- Many cases often resolve within 24 hrs of discontinuing the serotoninergic agent and initiating care
- But drugs with long half-lives or active metabolites may cause symptoms to persist
- Irreversible MAOIs carry the greatest risk, and symptoms can persist for several days
- SSRIs may contribute to the development of serotonin syndrome up to several weeks after drug discontinuation (e.g. the half-life of fluoxetine is 1 week and that of its metabolite norfluoxetine up to 2.5 weeks)

Serotonin Syndrome

- Supportive care:
  - Oxygen
  - IVF
  - Cardiac monitor
  - Correction of vital signs

Serotonin Syndrome

- Sedation:
  - Benzodiazepines for controlling agitation and correcting mild increase in blood pressure and heart rate
  - Diazepam prolongs survival in rat model of serotonin syndrome, but no specific agent has been studied in humans
  - Lorazepam 2-4mg iv/Diazepam 5-10mg iv, repeated every 8-10 minutes
  - Butyrophenones (e.g. Haloperidol) should be avoided because of anticholinergic properties that inhibit sweating and heat dissipation

Serotonin Syndrome

- Antidotes:
  - Cyproheptadine: H1 antagonist with nonspecific 5HT-1A and 5HT-2A antagonistic properties, and weak anticholinergic activity
  - Initial 12mg, followed by 2mg q2h, only in oral form
  - Definitive evidence of effectiveness is lacking
  - Antipsychotics with 5HT-2A antagonistic activity (e.g. Olanzapine, and Chlorpromazine); efficacy unproven, not recommended
  - Propranolol (long duration of action, may cause prolonged hypotension and mask tachycardia); Bromocriptine (serotonin agonist); Dantrolene (no effect on survival in animal models); they are not recommended

Serotonin Syndrome

- Control of autonomic instability:
  - For the severely intoxicated, large and rapid changes in blood pressure and heart rate are seen
  - For severe HT and tachycardia, treated with short-acting agents such as Esmolol or Nitroprusside
  - For hypotension from MAOIs, treated with low doses of direct-acting sympathomimetic amines (Phenylephrine, Adrenaline, or Noradrenaline); indirect agents (e.g. Dopamine) should be avoided because they are metabolised to Adrenaline and Noradrenaline, and when MAO inhibited, their production at the cellular level is not controlled ➔ exaggerated haemodynamic response

Serotonin Syndrome

- Control of autonomic instability:
  - Control of hyperthermia is critical, eliminating excessive muscle activity and minimising several severe complications: DIC, coma, seizures, hypotension, VT, and metabolic acidosis
  - No role for antipyretics (e.g. acetaminophen) because increased in BT is not due to an alteration in the hypothalamic temperature setpoint but rather to an increase in muscle activity

Serotonin Syndrome

- Prognosis
  - Generally favourable, as long as the entity is recognised and complications are treated appropriately
  - Reported morality rates ~ 11 to 25%

Case One

- Cyproheptadine was given as suggested by HKPIC
- Urine toxicology: Fluoxetine+ve (SSRI), Dothiepin+ve (TCA) with metabolites+ve
- GCS improved to 8/15 after Dormicum and Propofol infusions were stopped on 11/06/2013
- Haemodynamically stable
- Low grade fever, rising WCC 17, and CXR: RLZ infiltrate, and purulent tracheal aspirate
- Empirical Sulperazon started for chest infection

Case One

- 12/06/2013 morning, clinical deterioration with hypotension, dilated pupils (5mm), and GCS dropped to 3/15
- Inotrope for cardiovascular support
- Urgent CT brain (plain): severe diffuse cerebral oedema with transtentorial herniation
- Neurosurgical opinion was sought ➔ intervention no benefit
- CT cerebral venogram on 13/06/2013: filling defects at bilateral upper parts of internal jugular veins extending to sigmoid sinus, other parts of cerebral veins not well opacified and inconclusive ? due to significant cerebral oedema and raised ICP

Case One

- Thrombophilia screening was done for extensive cerebral vein thrombosis: lupus anticoagulant+ve; low levels of Protein C, Protein S, and anti-thrombin III
- ANF <80
- Comatose and clinical examination revealed absence of brainstem reflexes
- Radionuclide brain imaging on 18/06/2013 showed absence of brain perfusion and cerebral activity
- Ante-mortem blood test x toxicology showed high levels of Dothiepin and Fluoxetine

Case Two

- **Case two**
- 42/M
- Hx of substance dependence (hypnotics, benzodiazepines), with Hx of DO, rhabdomyolysis, and ARF precipitated by convulsion
- Repeated suicidal attempts
- Chronic hepatitis B
- c/o dizziness and restlessness, and admitted taking hypnotics
- Given iv medication in AED x agitation

Case Two

- Then admitted into Medical ward with stable vitals and **drowsiness**
- Later noted **sweating**, **high fever**, and **rigidity**
- U/O decreased and **blood x CPK as high as 30000** with ARF (Cr from 138 to 400)
- Cardiac arrest with VF, with defibrillation and Adrenaline shots given, and ROSC after 15min CPR
- In shock and tachycardia, on Dopamine infusion ~ 10ml/hr
- To ICU

Case Two

- **What is the diagnosis?**

Case Two

- Hx:

Neuroleptic Malignant Syndrome?

  - Drowsiness, sweating, high fever, and muscular rigidity
  - Serum CK level as high as 30000

Case Two

Diagnosis

Box 1: Clinical and laboratory features of neuroleptic malignant syndrome*

- The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
- Two or more of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leucocytosis, laboratory evidence of muscle injury (e.g., elevated creatinine phosphokinase).
- The symptoms are not due to another substance (e.g., phencyclidine) or a neurologic or other general medical condition.
- The symptoms are not better accounted for by a mental disorder (e.g., mood disorder with catatonic features).

Case Two

- Very desaturated requiring high MV support and on two high dose inotropes
- Anuric ARF due to rhabdomyolysis and CVVH started
- Treated as neuroleptic malignant syndrome with sedatives, bromocriptine, and muscle relaxant with continuous EEG monitoring
- Peak CPK >170000
- Poor GCS 5-6/15 after stopping all sedatives
- CT brain (plain): severe diffuse cerebral oedema

抗精神藥物惡性症候群

Neuroleptic Malignant Syndrome

- A life-threatening neurological emergency with the use of neuroleptic agents
- First described in 1960 by French physicians in a study involving Haloperidol whose side-effects were termed “syndrome malin des neuroleptiques”
- Characterised by a distinctive clinical syndrome of mental status change, rigidity, and dysautonomia
- Incidence rates range from 0.02 to 3% among patients taking neuroleptic agents
- Affects all age groups
- In most studies, men outnumber women 2x

Neuroleptic Malignant Syndrome

- Risk factors:
  - Use of higher doses of neuroleptic agents
  - Rapid escalation of dose
  - Parenteral therapy
  - Concomitant use of Lithium or other psychotropic drugs
  - Higher potency agents
  - Depot formulations
  - Comorbid substance abuse
  - Neurological diseases
  - Acute illness (including trauma, surgery, and infection)
  - Anti-parkinson medication withdrawal

Neuroleptic Malignant Syndrome

Box 2: Clinical manifestations of NMS

Physical findings

- Abnormal blood pressure (typically hypertension)*
- Altered level of consciousness*
- Chorea
- Diaphoresis*
- Fever (temperature > 38.5°C)*
- Generalized tonic-clonic seizures
- Muscle rigidity*
- Mutism
- Opisthotonos†
- Positive Babinski's sign
- Tachycardia*
- Tachypnea*
- Trismus‡

Laboratory findings

- ↑ Creatine kinase level*
- Leukocytosis, with shift to
- Myoglobinuria*
- ↑ Transaminase levels

*Common finding.

†Extreme hyperextension of the body in which the head and heels are bent backwar body is bowed forward.

‡Motor disturbance of the trigeminal nerve, especially spasm of the masticatory mus difficulty in opening the mouth.

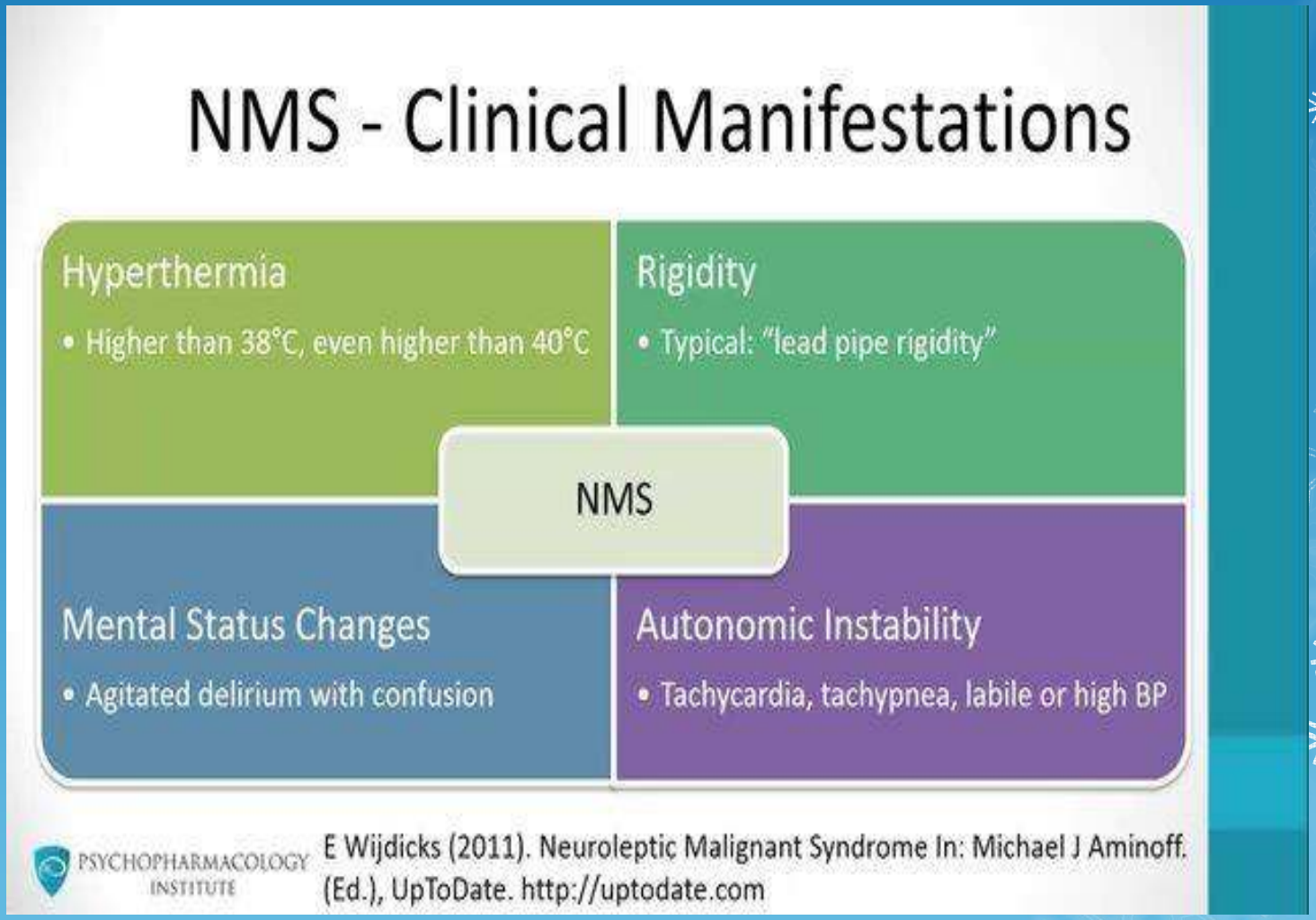
Medscape® www.medscape.com

Table 1. Neuroleptic malignant syndrome workup[a]

1. Complete blood count with differential
2. Serum electrolyte levels
3. Creatinine and blood urea nitrogen levels
4. Blood cultures
5. Urine cultures
6. Urine analysis to look for myoglobin
7. Serum creatine phosphokinase
8. Chest radiograph
9. Head CT scan to rule out other cause of confusion
10. Lumbar puncture to rule out central nervous system infection
11. Thyroid studies
12. Arterial blood gas, if pulmonary complications, to rule out pulmonary embolism

[a]*CT, computed tomography.*

Neuroleptic Malignant Syndrome



Neuroleptic Malignant Syndrome

- In an analysis of 340 cases, 70% of patients followed a typical course:
  - Mental status change appearing first
  - Followed by rigidity
  - Then hyperthermia, and autonomic dysfunction
- There is a substantial variability in the presentation of NMS

Neuroleptic Malignant Syndrome

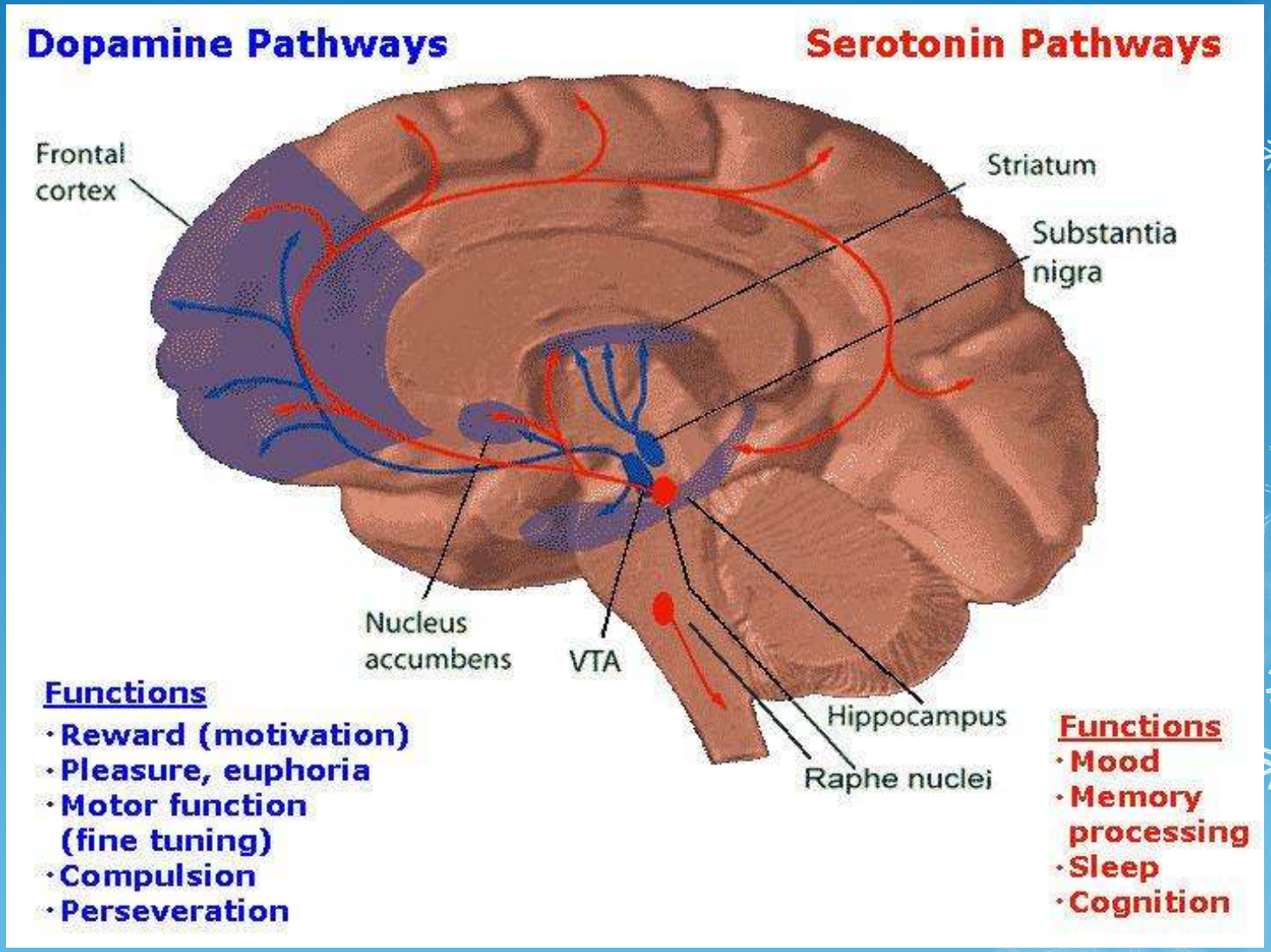
Box 1: Neuroleptic medications associated with neuroleptic malignant syndrome (NMS)*

Typical neuroleptics	*Atypical neuroleptics*
• Haloperidol (+++)	Clozapine (+)
• Chlorpromazine (++)	Olanzapine (+)
• Fluphenazine, long acting (++)	Quetiapine (+)
• Fluphenazine (++)	Risperidone (+)
• Levomepromazine (+)	
• Loxapine (+)	

*+ = rarely associated with NMS, +++ = more commonly associated with NMS.[1,8–14]

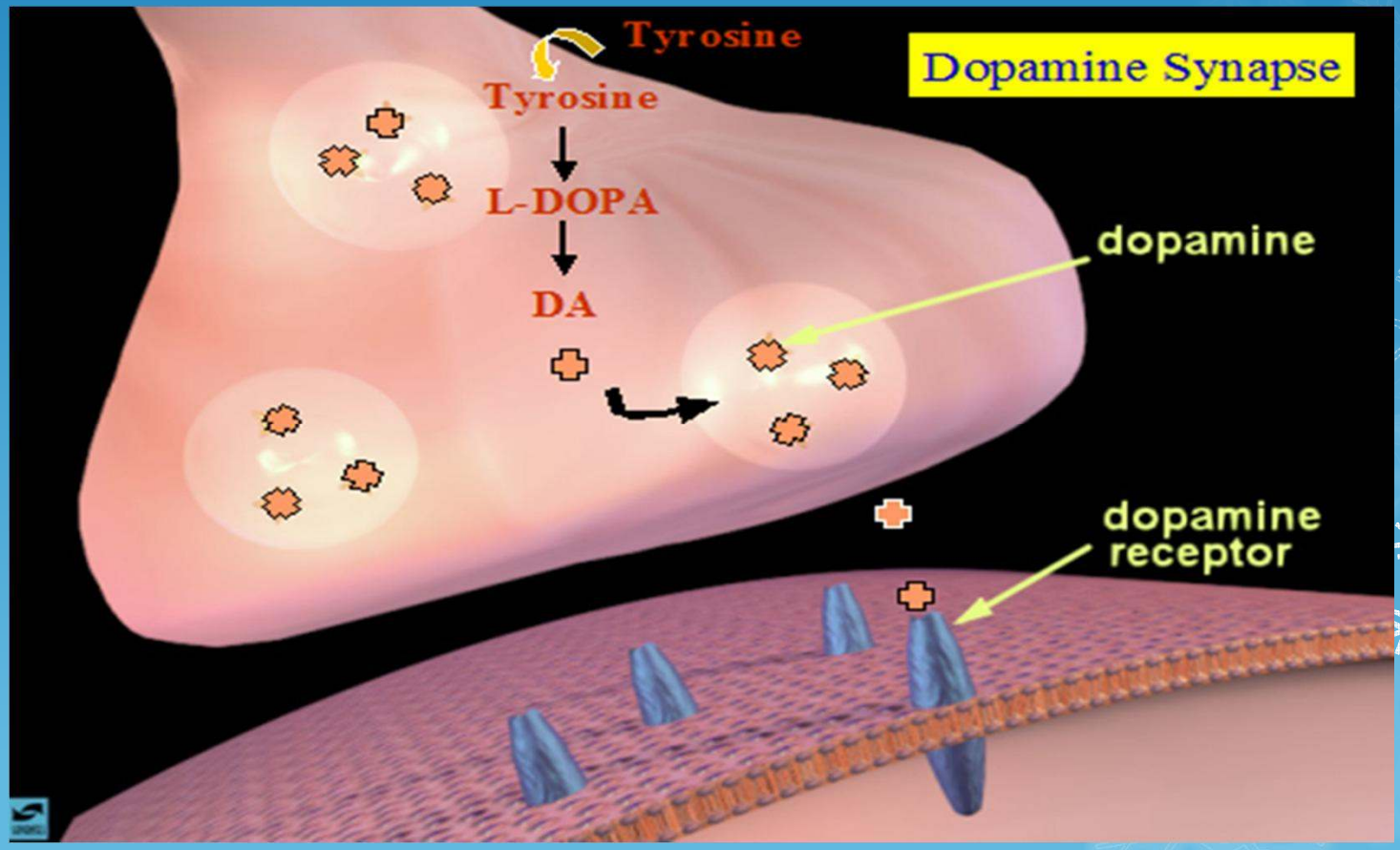
Anti-emetics:
Domperidone
Promethazine
Metoclopramide
Prochlorperazine

Neuroleptic Malignant Syndrome



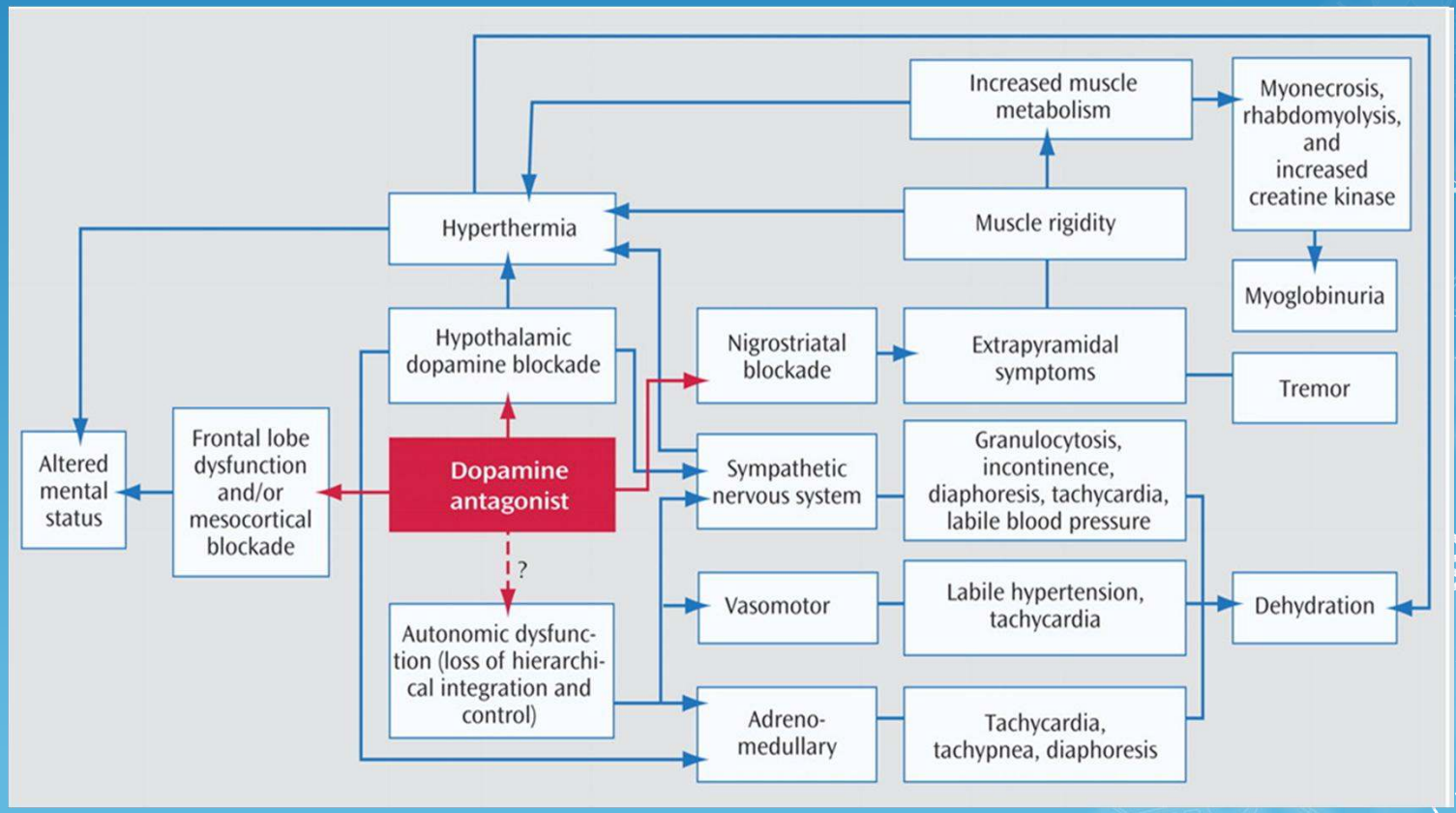
Neuroleptic Malignant Syndrome

- Dopamine receptors: D1 – D4



Neuroleptic Malignant Syndrome

- **Pathogenic mechanisms: anti-D2 receptors**



Neuroleptic Malignant Syndrome

Diagnosis

Box 1: Clinical and laboratory features of neuroleptic malignant syndrome*

- The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
- Two or more of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leucocytosis, laboratory evidence of muscle injury (e.g., elevated creatinine phosphokinase).
- The symptoms are not due to another substance (e.g., phencyclidine) or a neurologic or other general medical condition.
- The symptoms are not better accounted for by a mental disorder (e.g., mood disorder with catatonic features).

Neuroleptic Malignant Syndrome

- Mnemonic: **FEVER**
  - F – Fever
  - E – Encephalopathy
  - V – Vitals unstable
  - E – Elevated enzymes (elevated CK)
  - R – Rigidity of muscles

Neuroleptic Malignant Syndrome

TABLE 1. Differential Diagnosis of Neuroleptic Malignant Syndrome

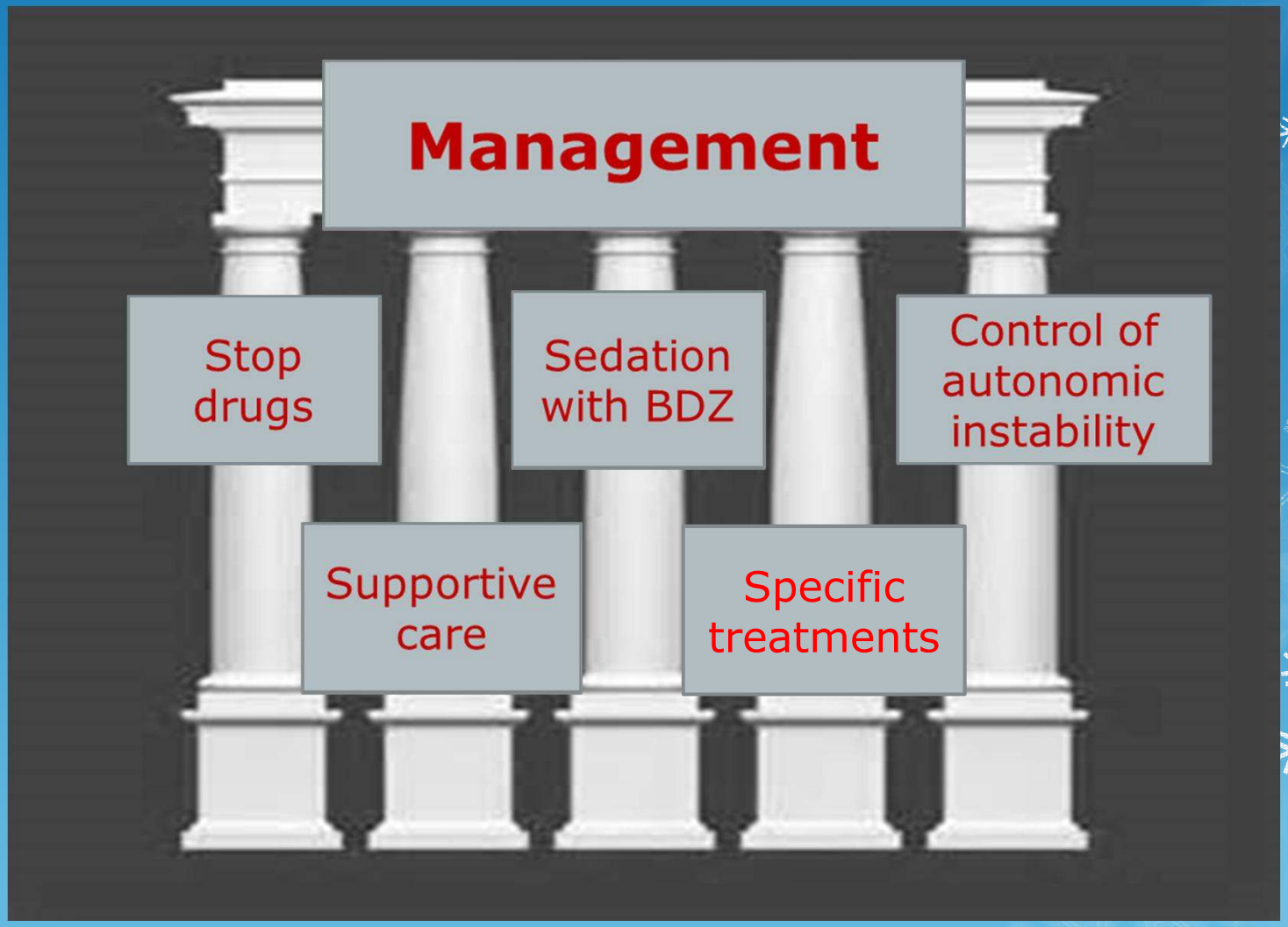
Infectious
Meningitis or encephalitis
Postinfectious encephalomyelitis syndrome
Brain abscess
Sepsis
Psychiatric or neurological
Idiopathic malignant catatonia
Agitated delirium
Benign extrapyramidal side effects
Nonconvulsive status epilepticus
Structural lesions, particularly involving the midbrain
Toxic or pharmacological
Anticholinergic delirium
Salicylate poisoning
Malignant hyperthermia (inhalational anesthetics, succinylcholine)
Serotonin syndrome (monoamine oxidase inhibitors, triptans, linezolid)
Substances of abuse (amphetamines, hallucinogens)
Withdrawal from dopamine agonists, baclofen, sedative-hypnotics, and alcohol
Endocrine
Thyrotoxicosis
Pheochromocytoma
Environmental
Heatstroke

Neuroleptic Malignant Syndrome

Box 4: Complications associated with NMS

- Rhabdomyolysis
- Acute renal failure
- Acute respiratory failure (pulmonary embolism, aspiration pneumonia)
- Seizures
- Brain damage
- Myocardial infarction
- Disseminated intravascular coagulation
- Hepatic failure
- *Escherichia coli* fasciitis
- Sepsis

Neuroleptic Malignant Syndrome



Neuroleptic Malignant Syndrome

- Specific treatments: based on case repor
  experience, not on data from clinical trial
  - Dantrolene: a direct-acting skeletal muscle relaxant, effective in treating malignant hyperthermia
  - Doses of 1-2.5mg/kg iv, repeated to a maximum dose of 10mg/kg/day
  - Effect includes reduction of heat production and rigidity, within minutes of administration
  - Risk of hepatotoxicity
  - Discontinuing it after a few days; continuing for 10 days followed by a slow taper

Neuroleptic Malignant Syndrome

- Specific treatment:
  - Bromocriptine: a dopamine agonist, to restore lost dopaminergic tone
  - Well tolerated in psychotic patients
  - Doses of 2.5mg (through NG tube) q6-8h, up to a maximum dose of 40mg/day
  - Continuing for 10 days followed by slowly tapering
  - Amantadine has dopaminergic and anticholinergic effects, alternative to bromocriptine
  - Dose of 100mg orally or via NG tube, to a maximum dose of 200mg q12h

Neuroleptic Malignant Sy

- Electroconvulsive therapy (ECT):
  - The rationale of the use in NMS: its efficacy in treating malignant catatonia
  - No prospective, randomised controlled data supports its use
  - Safety concerns: seizure, cardiovascular complications, and risk of general anaesthesia
  - Generally reserved for patients not responding to other treatments

Neuroleptic Malignant Syndrome

- Prognosis:
  - Most cases resolve within 2 weeks
  - Reported mean recovery times are 7 to 11 days
  - But cases persisting for 6 months with residual catatonia and motor signs are reported
  - Risk factors for a prolonged course: depot antipsychotic use and concomitant structural brain disease
  - Most patients recover without neurological sequelae
  - Reported mortality rates are 5 to 20%
  - Disease severity and occurrence of complications are the strongest predictors of mortality

Take Home Message

- Both serotonin syndrome and neuroleptic malignant syndrome, though rare, can be life-threatening
- Have similarities and differences clinically and biochemically
- Both diagnoses made on clinical grounds
- Managements include drug discontinuation, supportive care, sedation, control of autonomic instabilities, and some specific treatments
- Prognosis usually favourable
- Detailed drug history and high index of suspicion important!

Take Home Message

Clinical differences	NMS	Serotonin syndrome
Precipitating factors	Sudden withdrawal of dopaminergic agents or introduction of agents that block dopamine signaling (eg, neuroleptics and antiemetics)	Combination of agents that potentially stimulate serotonin receptors such as SSRIs and MAOIs
Onset	Slower; 3-9 days following an addition of a neuroleptics	Sudden, within 24 h (in 75% of cases) following the addition of a serotonergic agent
Mental status	Stupor, alert mutism, coma	Agitation, coma
Autonomic symptoms	Hyperthermia (>38°C)	Dilated pupils, diarrhea, diaphoresis, vomiting
Neuromuscular symptoms & signs	Akinesia, extrapyramidal rigidity	Shivering, ataxia, myoclonus, hyperreflexia, ankle clonus, Barbinski sign, nystagmus
Elevation of WBC, LFT and muscle enzymes	Common	Less frequently
Recovery	Slower, days to weeks	Rapid, 70% within 24 h
Mortality	15-20%	2.5%


Thank You
"A Real Jolter – Not For The Faint Of Heart."
–Kevin Thomas, LOS ANGELES TIMES