NEUROLEPTIC MALIGNANT SYNDROME

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Some definitions

- *Neuroleptic :* Any of a class of psychotropic drugs used to treat psychosis, particularly schizophrenia.
- *Antipsychotic medication :* Denoting the actions of such an agent (e.g. chlorpromazine), a neuroleptic. used in the treatment of schizophrenia and psychosis.
- *Atypical Antipsychotic agent:* Medications (also neuroleptics) used in the treatment of schizophrenia and psychosis. Referred to as second-generation anti-psychotics (SGA) or serotonin-dopamine antagonists (SDA). First appeared in 1986. Tend to have a lower incidence of tardive dyskinesia and extrapyramidal symptoms (EPS)

Some definitions

- *Extra Pyramidal Symptoms (EPS):* Abnormal, involuntary movements attributed to pathologic states of one or more parts of the **striate body** and characterized by insuppressible, stereotyped, automatic movements (e.g. rigidity, tremors, shuffling gait, or posturing) that cease only during sleep.

What is NMS?

- A rare but life-threatening idiosyncratic reaction to ***a neuroleptic medication*** characterized by:
  - Mental status changes
  - Severe muscle rigidity
  - Fever
  - Autonomic instability
- Mortality estimated to be 10-20%

Historical Perspective

- 1832 – Carmeil described patients who were agitated, psychotic, stuporous → died with hyperthermia
- 1849 – Bell reported on a disorder he found in 40 of 1700 patients admitted to the McLean Asylum (now McLean Hospital, Boston) over 12 years, psychotic, agitated, febrile, delirious, tremulous, tachycardic → died
- 1934 – Stauder coined the term lethal catatonia for the disorder

Historical Perspective

- 1947 – Adland published a detailed review of the literature – acute exhaustive psychoses for the previous terms used : acute delirium,fatal catatonia, acute dementia praecox, manic depressive exhaustive death, acute idiopathic psychosis, brain death in schizophrenia, Scheid's catatonic syndrome, Bell's mania

Historical Perspective

- Adland said in 1947:

"This present author believes that this illness originates as a psychogenic problem and that the psychopathology – the dynamic of the disorder – is expressed though dysfunctions of the cardiovascular, heat regulatory and hematopoietic systems

Historical Perspective

- Advent of neuroleptic treatment in Europe in 1950's
- Extrapyramidal symptoms (rigidity, tremors, dystonia, akinesia, akathisia) + stupor + extreme high Temp + pulmonary complications
- First definition : 1960's French Psychiatrists Delay & Deniker defined the syndrome associated with the use of neuroleptics
- Term coined : **"syndrome malin des neuroleptiques"**

  (Neuroleptic Malignant Syndrome)

Historical Perspective

- 1973 – Melzter → Described a case of NMS with CPK elevation → CPK became an important marker
- 1977 – Gelenberg and Mendel called attention to the ability of high potency neuroleptic drugs to cause catatonic reactions
- 1980 Caroff – extensive review – turning point of establishment of NMS criteria
- 1985 Levenson developed first criteria

Etiology & Pathophysiology

- Occur in association with *antipsychotic medications*
- most commonly linked to "typical" antipsychotics such as haloperidol, may also occur with atypical neuroleptics such as risperidone and olanzapine or antiemetics such as promethazine
- Genetic factors also might play a role. Case reports have been published on neuroleptic malignant syndrome occurring in identical twins as well as in a mother and 2 of her daughters
- There are five known types of dopamine receptors; D1, D2, D3, D4, and D5.
- It is believed to occur from **dopamine D2 receptor blocking agents or dopamine depleting agents**.

Etiology & Pathophysiology

"The most compelling evidence supports the occurrence of **central dopamine *hypo*activity** as the principal factor in the development of NMS" (Man et al 2003)

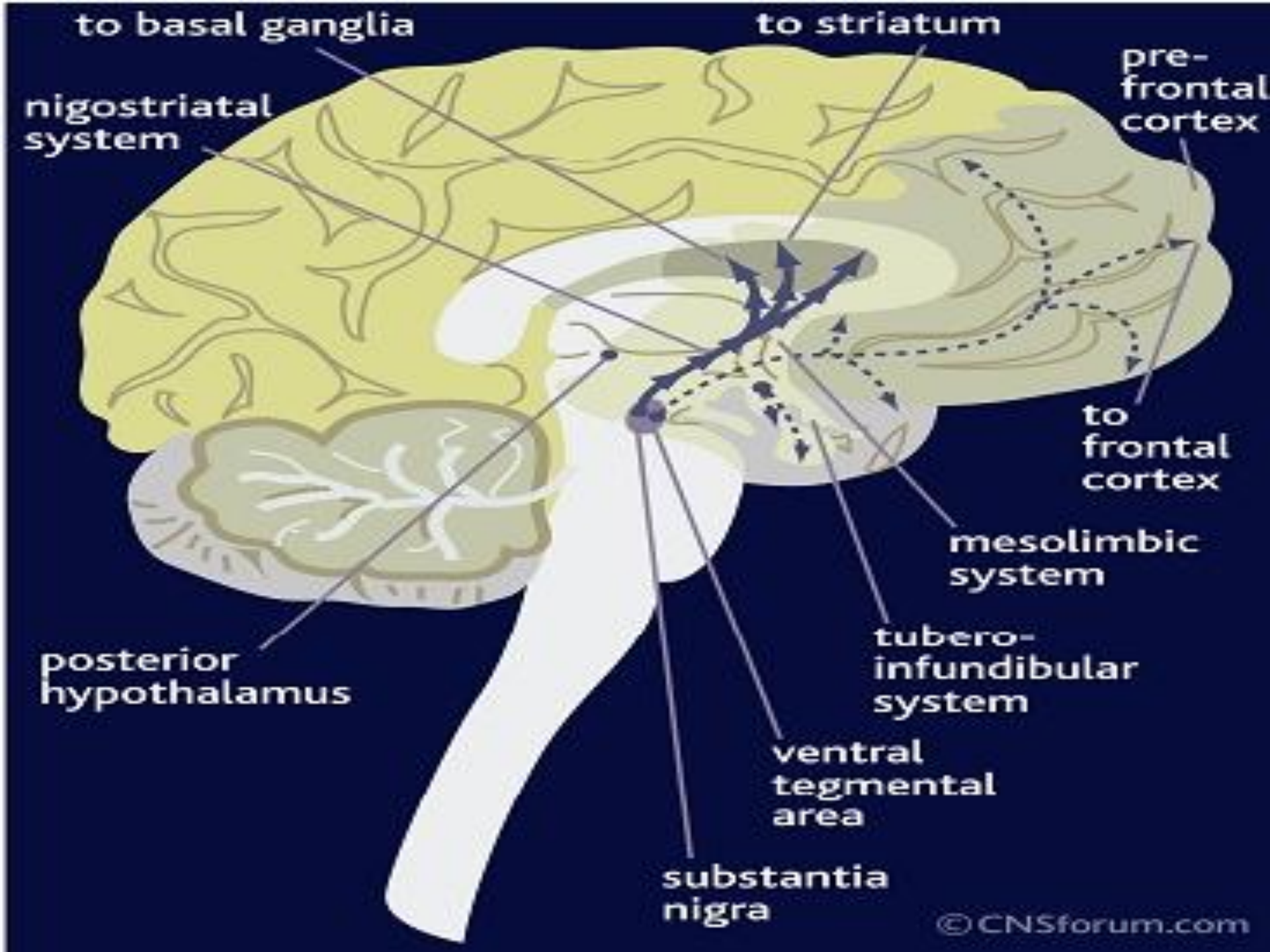
Etiology & Pathophysiology

1. a relative imbalance of norepinephrine to dopamine in the CNS
2. serotonergic imbalances
3. excessive catecholamine secretion (Susman, 2001)
4. previous studies suggest altered calcium and iron metabolism. (Gurrera 1999)
5. implicated norepinephrine dysregulation of the sympathetic nervous system.

Etiology & Pathophysicology

"There is a **lack of consensus** on pathophysiological background of NMS, and in spite of some meta-analyses it seems that the knowledge on treatment options for NMS is dominantly based on case report experiences. Accordingly, a lack of consensus on treatments for NMS should not be surprising"

(Margetic et al, 2010, review)


to basal ganglia
to striatum
pre-
frontal
cortex
nigostriatal
system
to
frontal
cortex
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tubero-
infundibular
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posterior
hypothalamus
ventral
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area
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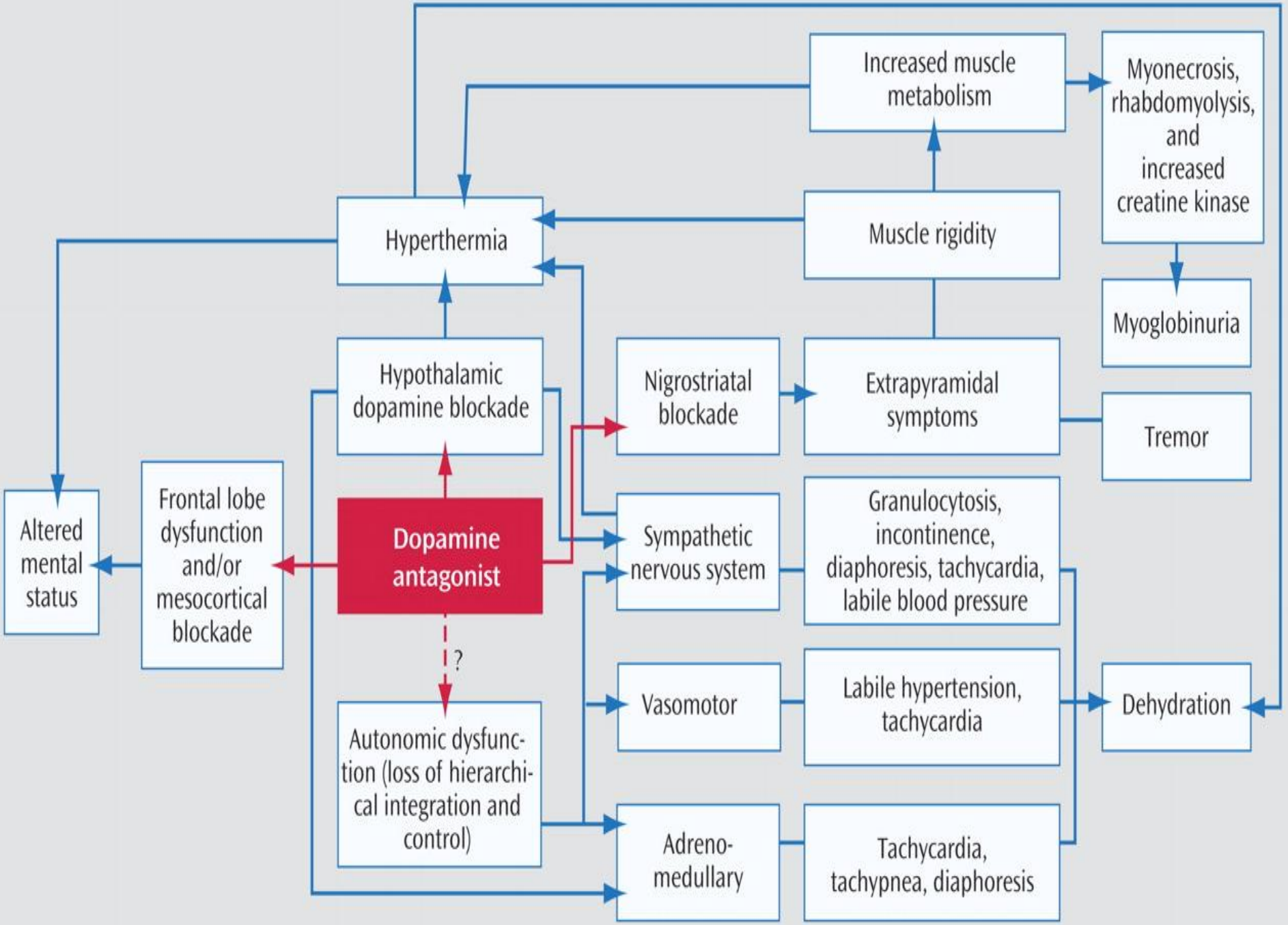
Increased muscle metabolism
Myonecrosis, rhabdomyolysis, and increased creatine kinase
Hyperthermia
Muscle rigidity
Myoglobinuria
Hypothalamic dopamine blockade
Nigrostriatal blockade
Extrapyramidal symptoms
Tremor
Altered mental status
Frontal lobe dysfunction and/or mesocortical blockade
Dopamine antagonist
Sympathetic nervous system
Granulocytosis, incontinence, diaphoresis, tachycardia, labile blood pressure
?
Vasomotor
Labile hypertension, tachycardia
Dehydration
Autonomic dysfunction (loss of hierarchical integration and control)
Adreno-medullary
Tachycardia, tachypnea, diaphoresis

Etiology : "known agents"

- **Phenothiazines:** Mellaril, Compazine, Thorazine, Phenergan, Prolixin
- **Butyrophenones:** Haldol, Inapsine
- **Thioxanthenes:** Navane

Dibenzepines: Zyprexa, Clozaril

Benzisoxazoles: Risperdal

- **Dopamine Antagonists:** Reglan, Vistaril , Reserpine
- **Anti-Parkinson's Agents:** (NMS may occur from sudden withdrawal of these) Amantadine , Levodopa , Lithium , Bromocriptine

Conventional Antipsychotic Drugs:	
chlorpromazine	Thorazine
pimozide	Orap
haloperidol	Haldol
loxapine	Loxitane
mesoridazine	Serentil
molindone	Moban
perphenazine	Trilafon
thioridazine	Mellaril
thiothixene	Navane
trifluoperazine	Stelazine

Atypical Antipsychotic Drugs:	
aripiprazole	Abilify
clozapine	Clozaril
Oolanzapine	Zyprexa
quetiapine	Seroquel
risperidone	Risperdal
ziprasidone	Geodon
Dopamine Antagonists in Medical Settings	
droperidol	Inapsine
metoclopramide	Reglan
prochlorperazine	Compazine
promethazine	Phenergan

Etiology : risk factors

- Organic brain syndrome
- Bilateral frontal lesions
- Mental retardation
- Affective disorders
- Warm and humid environment, Dehydration, exhaustion
- Rapid or parenteral administration of antipsychotic agents
- Rapid increase in neuroleptic dose
- Agitation or catatonia
- Recent episode of catatonia
- Prior episode of NMS
- Past hx of ECT treatment
- Post-Partum Period
- Use of Lithium or an anticholinergic along with a “known agent”
- Male:female → 2:1

Incidence

- The frequency has been variably reported as 0.07–2.2% of patients taking neuroleptics. Data largely come from case control studies rather than prospective randomized trials
- Higher in males
- Rare in children
- Higher <age 40

Clinical Tetrad

1. Mental status changes:
   - Initial symptom in 82%
   - Agitated delirium with confusion
   - Catatonic signs
   - Mutism
   - Evolution to profound encephalopathy and coma is typical
2. Muscular rigidity
   - "Lead pipe rigidity" throughout range of motion
   - Superimposed tremor
   - Sialorrhea, dysarthria, dysphagia
3. Hyperthermia (as high as 107.6 F with a mean of 103 F)
4. Autonomic instability
   - Tachycardia most common
   - Labile blood pressure
   - Tachypnea
   - Diaphoresis

Onset

- **Two thirds** of cases occur **within the first week.**
- May occur as soon as **within 24 hours** of the first dose of antipsychotic medication
- The average onset appears to be **between 48 to 72 hours**
- May occur **at any time** during the course of treatment.

Varying Diagnostic Criteria for Neuroleptic Malignant Syndrome

DSM-IV-TR Criteria[5] (Both from A and at least 2 from B)	**Adityanjee Criteria**[6] (All 4 major and at least 2 from autonomic dysfunction category)	**Levenson Criteria**[4] (All 3 major symptoms, or 2 major symptoms and 4 minor symptoms)	**Pope Criteria**[3] (All 3 required) Retrospective: 2 of 3 with additional criteria
Criteria A 1. Muscle rigidity 2. "Fever" *Criteria B* -Diaphoresis -Dysphagia -Tremor -Incontinence -Altered consciousness -Mutism -Tachycardia -Elevated or labile BP -Leukocytosis -Lab evidence of muscle injury *Criteria C* Not due to other cause (eg, viral encephalitis) *Criteria D* Not due to mental disorder	*Major Features* 1. Altered sensorium (except agitation) documented by 2 different observers 2. Muscle rigidity 3. Hyperthermia (> 39°C oral) 4. Autonomic dysfunction -Tachycardia (> 90/min) -Tachypnea (> 25/min) -BP fluctuation of at least 30 mm Hg systolic or 15 mm Hg diastolic -Diaphoresis -Incontinence *Supportive Features* 1. CPK elevation 2. Leukocytosis	*Major Symptoms* 1. "Fever" 2. Muscle rigidity 3. Elevated CPK *Minor Symptoms* -Tachycardia -Abnormal BP -Tachypnea -Altered consciousness -Diaphoresis -Leukocytosis	*Major Criteria* 1. Hyperthermia (> 37.5°C) 2. Severe EPS (2 or more) -Lead-pipe rigidity -Cogwheeling -Sialorrhea -Oculogyric crisis -Retrocollis -Opisthotonos -Trismus -Dysphagia -Choreiform movements -Dyskinetic movements -Festinating gait -Flexor-extensor posturing 3. Autonomic dysfunction (2 or more) -Hypertension ≥ 20 mm Hg rises DBP -Tachycardia ≥ 30 above baseline -Tachypnea ≥ 25 -Diaphoresis -Incontinence *Retrospective Criteria* 1. Clouded consciousness 2. Leukocytosis (> 15,000) 3. CPK > 300 U/L

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders (fourth edition-text revision); EPS = extrapyramidal symptoms; CPK = creatine phosphokinase; BP = blood pressure; DBP = diastolic blood pressure.

Symptoms & Signs Overview

- A mnemonic used to remember the features of NMS is FEVER.
- **F** – Fever
- **E** – Encephalopathy
- **V** – Vitals unstable
- **E** – Elevated enzymes (elevated CPK)
- **R** – Rigidity of muscles

Revised mnemonic for NMS: FALTER

- **F** – Fever
- **A** – Autonomic instability
- **L** – Leukocytosis
- **T** – Tremor
- **E** – Elevated enzymes (elevated CPK)
- **R** – Rigidity of muscles

Lab findings : cascade

- Muscle contraction
- Rhabdomyolysis, myonecrosis
- Myoglobinuria, CPK levels
- Renal Failure
- Diaphoresis, Dehydration, Incontinence, Leukocytosis
- Hypokalemia, Hyponatremia, Hypocalcemia,Hypomagnesemia

Lab findings

- Elevated CPK in 95% of NMS cases
- Can reach 100,000 IU/L
- Myoglobinuria in 67% of reported NMS cases
- Lactic acidosis (2/2 myglobinuria)
- Transaminase elevations (2/2 myglobinuria)
- Aldolase elevations (2/2 myglobinuria)
- Metabolic acidosis (%75 of reported NMS cases)
- Leukocytosis (with or without a left shift) presents as a secondary response to stress or tissue damage

Lab findings

- Increased LDH
- Increased AST
- Increased ALT
- Increased alkaline phosphatase
- Hyperuricemia
- Hyperphosphatemia
- Myoglobinemia
- Leukocytosis
- Thrombocytosis
- Proteinuria
- Decreased serum iron
- Increased cerebrospinal fluid (CSF) protein
- Hypocalcemia
- Myoglobinuria

Prognosis

- Most series suggest that the mortality rate is 10-20%. When reporting bias is factored in, the true rate of mortality from neuroleptic malignant syndrome might be much lower.
- Mortality rates generally are higher in patients who develop severe muscle necrosis and resulting rhabdomyolysis.

Associated complications

- Rhabdomyolysis- from sustained muscle contraction
- Renal Failure-secondary to myonecrosis
- Respiratory failure, pulmonary embolism, and aspiration pneumonia- from chest wall rigidity
- Hepatic Failure
- Myocardial infarction, arrhythmias, and cardiac arrest- from altered cardiac conduction
- Thromboembolism-from immobility and hyperthermia.
- Aspiration
- Infection
- Seizures-from hyperthermia

Neuroleptic Malignant Syndrome Work-Up

(Items in part determined by patient's presentation)

1. Complete blood count with differential
2. Serum electrolyte levels and liver function test (comprehensive metabolic panel)
3. Blood cultures
4. Urine cultures
5. Urinalysis to look for myoglobin
6. Serum creatine phosphokinase
7. Chest radiograph
8. Head CT scan to rule out other cause of confusion
9. Optional abdominal and/or pelvic CT scan to rule out abscess
10. EEG to rule out seizure or postictal state causing confusion
11. Lumbar puncture to rule out central nervous system infection
12. Thyroid studies
13. Ammonium level to rule out as a cause of mental change
14. Arterial blood gas, if pulmonary complications, to rule out pulmonary embolism
15. Serum iron levels (low levels predict poorer prognosis)

CT = computed tomography; EEG = electroencephalogram.

Differential Dx

NMS is a *diagnosis of exclusion*

- ***Serotonin syndrome***
- ***Lethal catatonia***
- *Central nervous system (CNS) infection*
- ***Malignant Hyperthermia***
- *Heatstroke*
- *Encephalitis*
- *Thyrotoxicosis*
- *Drug intoxication*

Diff Dx: Lethal Catatonia

- Also called "malignant catatonia"
- Virtually indistinguishable from NMS
- Prodromal phase; noted by mood lability and lasting about 2 weeks.
- Progresses to a hyperactive or psychotic excitement phase lasting about 7 days, then finally to exhaustion or death.
- Can occur **with or without** neuroleptic exposure.
- **Common causes include:** head trauma, tumors, schizophrenia, cerebrovascular disorders, seizure disorders, metabolic disorders, toxic states (e.g. lead poisoning), and CNS infections.

Management : Protocol

- Discontinue the offending agent !
- Airway management: intubation for airway protection, continuous pulse- oximetry, adequate oxygenation and ventilation.
- Transfer to ICU !
- Circulatory support: cardiac monitoring, fluid resuscitation, hemodynamic support
- Cooling measures: cooling blankets, bathing, fans

Management : Protocol

- Screening for infections: head CT, lumbar puncture, blood and urine cultures
- Toxicology screen
- Avoid anticholinergic agents !
- *Amantadine* for hyperthermia, 100mg BID, oral or NGT
- *Bromocriptine* for hyperthermia, 2.5-10mg TID, oral or NGT
- *Dantrolene Sodium* for muscular rigidity and hyperthermia, 2-3 mg/kg , IV every 6 hours (to a maximum dose of 10mg/kg per 24 hours).
  - Bottoni (2002)

Management

- *Dantrolene sodium* administered intravenously remains the gold standard for treatment of muscular rigidity.
- Dantrolene inhibits excess calcium release, relaxing skeletal muscle. This relaxed state may help to reduce the hyperthermic state
- The adjunct of dopamine agonists may be warranted. *Bromocriptine, levodopa, and amantadine* have shown to be effective in the management of NMS and potentially shorten the course of illness

Management

- The use of benzodiazepines in the treatment of NMS is controversial
- Respiratory Depression ? Contributing agent?
- Helpful for agitation, if bz are to be used respiratory monitorization is crucial !
- Medications should be administered intravenously or per nasogastric tube as much as possible.
- Oral medications *should not be administered* if thoracic or esophageal dystonias are present, as aspiration may occur.

Management

- Bathing and cooling blankets help reduce hyperthermia
- The use of antipyretics is controversial
- Massage may be used to increase peripheral vasodilation.
- Antiembolic stockings and low dose Lovenox can help reduce the formation of deep vein thrombosis.
- Chest physiotherapy, range of motion exercises and frequent turning and repositioning are needed to help relieve immobility and rigidity.

Management

- Some data suggest that electroconvulsive therapy is effective for neuroleptic malignant syndrome, but serious treatment-related complications have occurred
- Specifically, patients with neuroleptic malignant syndrome have developed cardiac arrest and ventricular fibrillation after electroconvulsive therapy.

(Tongonogy, 2001)

Dantrolene

- Stimulates muscle relaxation by modulating skeletal muscle contractions at a site beyond myoneural junction and by acting directly on the muscle itself.
- Can be administered PO/IV. IV form is much more expensive and should be reserved for patients unable to take oral medications
- 100-200 mg/d PO; not to exceed 400 mg/d 0.8-2.5 mg/kg IV q6h; not to exceed 10 mg/kg/d

Dantrolene

- Might cause hepatotoxicity (use only for recommended indications); caution in impaired pulmonary function and severe cardiac insufficiency; might cause photosensitivity with exposure to sunlight
- Coadministration of clofibrate and warfarin can increase toxicity; coadministration with estrogen can increase hepatotoxicity in women >35 y

Medication rechallenge

- Patients may begin antipsychotic therapy after complete resolution of symptoms.
- 2-week "washout" period of all medications elapse after full resolution from NMS, before rechallenging (Bottoni 2002)
- **A low-dose, low-potency** neuroleptic from a **different chemical class** should be selected.
- Titration of the antipsychotic should be performed slowly.
- A benzodiazepine may be added to help decrease agitation. The patient must be monitored closely for relapse or side effects
- Should NMS recur, prompt withdrawal of the offending agent and treatment for NMS must be re-instituted

Medication rechallenge

- If patients are rechallenged with antipsychotics within 2 weeks of an episode of neuroleptic malignant syndrome, 63% will have a recurrence.
- If more than 2 weeks have elapsed, only 30% will have a recurrence.
- Eighty-seven percent of patients who develop neuroleptic malignant syndrome will be able to tolerate an antipsychotic at some point in the future.

(Tongonogy, 2010)

Prevention

- **Early recognition of extrapyramidal and catatonic symptoms** should alert the prescriber for dosage reduction and clinical reassessment.
- Velamoor (1998) suggests reduction in agitation with the use of benzodiazepines, and **avoidance of frequent parenteral injections.**
- Adequate hydration, good nutrition and routine exercise are also recommended for prevention.

NMS Controversies

- There are controversies associated with virtually all important aspects of NMS.
- NMS is usually defined as an idiosyncratic reaction, although the main postulated mechanisms for the development of NMS are linked to the pharmacological characteristics of drugs.
- There is no single set of criteria that is unanimously accepted.
- There is an important gap between the research of NMS and clinical practice

(Margetic et al, 2010, review)

Medicolegal Pitfalls

- When a patient develops neuroleptic malignant syndrome, especially when the result is fatal, physicians can be sued.
- Predicting who will develop neuroleptic malignant syndrome essentially is impossible given the current state of medical technology.
- Knowing that men younger than 40 years and those who previously have had neuroleptic malignant syndrome are at somewhat higher risk might help in risk stratification.

(Tongonogy, 2010)

Medicolegal Pitfalls

- Informed consent is particularly important before initiating treatment in these populations. Unfortunately, therapy with neuroleptics often is begun when patients are least likely to hear and interpret information accurately for informed consent, which presents a difficult area medicolegally because neuroleptic malignant syndrome is a rare but serious complication of neuroleptic therapy.
- The safest course is to provide patients and their families with as much information as they can absorb and follow up with additional information. This can be difficult to achieve in an often less-than-ideal setting.

(Tongonogy, 2010)

Patient education

Helpful Web Sites:

- Neuroleptic Malignant Syndrome Information Service
- NINDS Neuroleptic Malignant Syndrome Information Page
- WebMD, Neuroleptic Malignant Syndrome

Case example

An 81-year-old man with a history of schizoaffective disorder presented to hospital with increasing auditory hallucinations, persecutory delusions and depressive symptoms, including suicidal ideation. He was admitted to hospital and given loxapine (10 mg every morning, 50 mg every evening) for his psychotic symptoms and methotrimeprazine (10 mg once daily) for sleep disturbance. Two weeks earlier he had been prescribed venlafaxine by his family physician and had been experiencing some symptomatic hypotensive episodes as a result. He had also been taking levothyroxine (0.1 mg once daily) and procyclidine (2.5 mg once daily).

Within 3 days after admission, the methotrimeprazine therapy was stopped because of somnolence and the loxapine dose increased to 65 mg/d at bedtime. Twelve hours after this change, the patient had diaphoresis, tremulousness, urinary incontinence and some cognitive impairment. His temperature was elevated (38.3°C), and although normotensive (blood pressure 124/84 mm Hg) he had tachycardia (heart rate 128 beats/min) and exhibited Parkinsonian features, including tremor, rigidity and unsteady gait. An electrocardiogram revealed no acute ischemic changes.

Laboratory investigation revealed mild leukocytosis (leukocyte count 11.7 x 10^9/L), with a shift to the left (neutrophil count 9.9 x 10^9/L). His aspartate aminotransferase level was elevated (82 U/L), and his creatine kinase (CK) level was markedly elevated (1145 U/L), with normal CK MB fraction and cardiac troponin levels. Other laboratory results, including electrolyte levels, were normal.

The patient was observed for the night. The next morning his Parkinsonian features and elevated temperature persisted, and he was found to have bilateral hyporeflexia. The loxapine therapy was stopped because neuroleptic malignant syndrome (NMS) was suspected. That afternoon the CK level climbed to 2574 U/L. The next day, the patient had increased rigidity and his temperature rose to 39.3°C. A septic workup yielded normal results, but the urine myoglobin test result was positive. A firm diagnosis of NMS was made, and therapy with dantrolene (70 mg intravenously) was started and about 24 hours later was changed to bromocriptine (2.5 mg 3 times daily).

Within a few days, the patient's NMS symptoms improved and his CK level returned to normal. As his symptoms resolved, the bromocriptine dose was tapered off. In order to control his ongoing psychotic symptoms, the patient was prescribed olanzapine (2.5 mg once daily) because of its lower reported rate of NMS. He was also given sertraline (25 mg once daily) to control his depressive symptoms. After 5 weeks, his depressive and psychotic symptoms improved considerably, and he was discharged from hospital without further complications.

Questions

- **Which is NOT an intervention in the management of *neuroleptic malignant syndrome?***

A. Discontinuation of the antipsychotics
B. Use of bromocriptine/amantadine
C. Use of lorazepam to treat catatonia
D. Use of haloperidol to control agitation

Questions

A schizophrenic patient on treatment with *pimozide* reports that he cannot keep still and feel a compulsion to move. These symptoms are characteristics of

- A. Acute dystonia
  B. Drug-induced Parkinsonism
  C. Akathisia
  D. Neuroleptic Malignant Syndrome
  E. Serotonin syndrome

SEROTONIN SYNDROME

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What is SS?

- Serotonin syndrome is an acute **iatrogenic** drug induced condition, characterised by a triad of
  - cognitive behavioral changes
  - autonomic instability
  - neuromuscular excitability.
- It is caused by **overstimulation** of 5-hydroxytryptamine (5-HT) receptors.

Historical perspective

- First described in 1959 in a patient with tuberculosis who received meperidine.
- His death was described as “fatal toxic encephalitis.”
- The patient exhibited clonus, severe muscular hyperactivity,and rigidity.
- It was later discovered that patients on a monoamine oxidase inhibitor (MAOI) who took tryptophan developed an unsteady gait, clonus, tremor,incoordination, lightheadedness, paresthesias, CNS excitation, dilated pupils, and hyperactive reflexes.

Historical perspective

- In 1982, the term Serotonin Syndrome was used to describe the constellation of symptoms observed with administration of two or more medications that elevated serotonin concentrations

Etiology & Pathophysiology

- Serotonin is formed in biologic systems from the amino acid L-tryptophan
- Once formed, it is stored or rapidly inactivated by monoamine oxidase
- Over **90%** of the serotonin in the body is found in enterochromaffin cells **in the GI tract.**
- Abnormally elevated concentrations of serotonin and clinical signs and symptoms of serotonin syndrome develop because of drug induced serotonin augmentation.

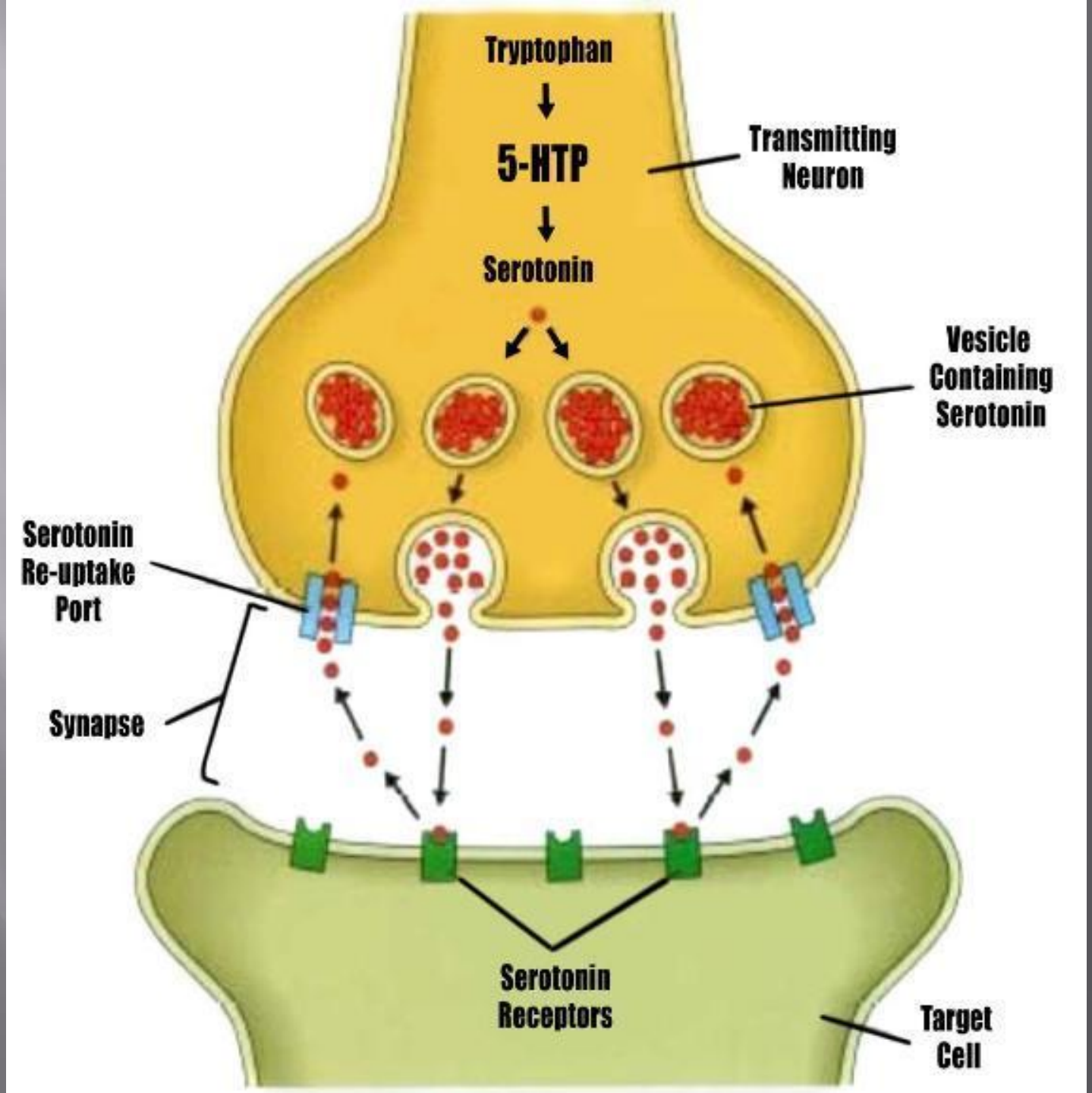
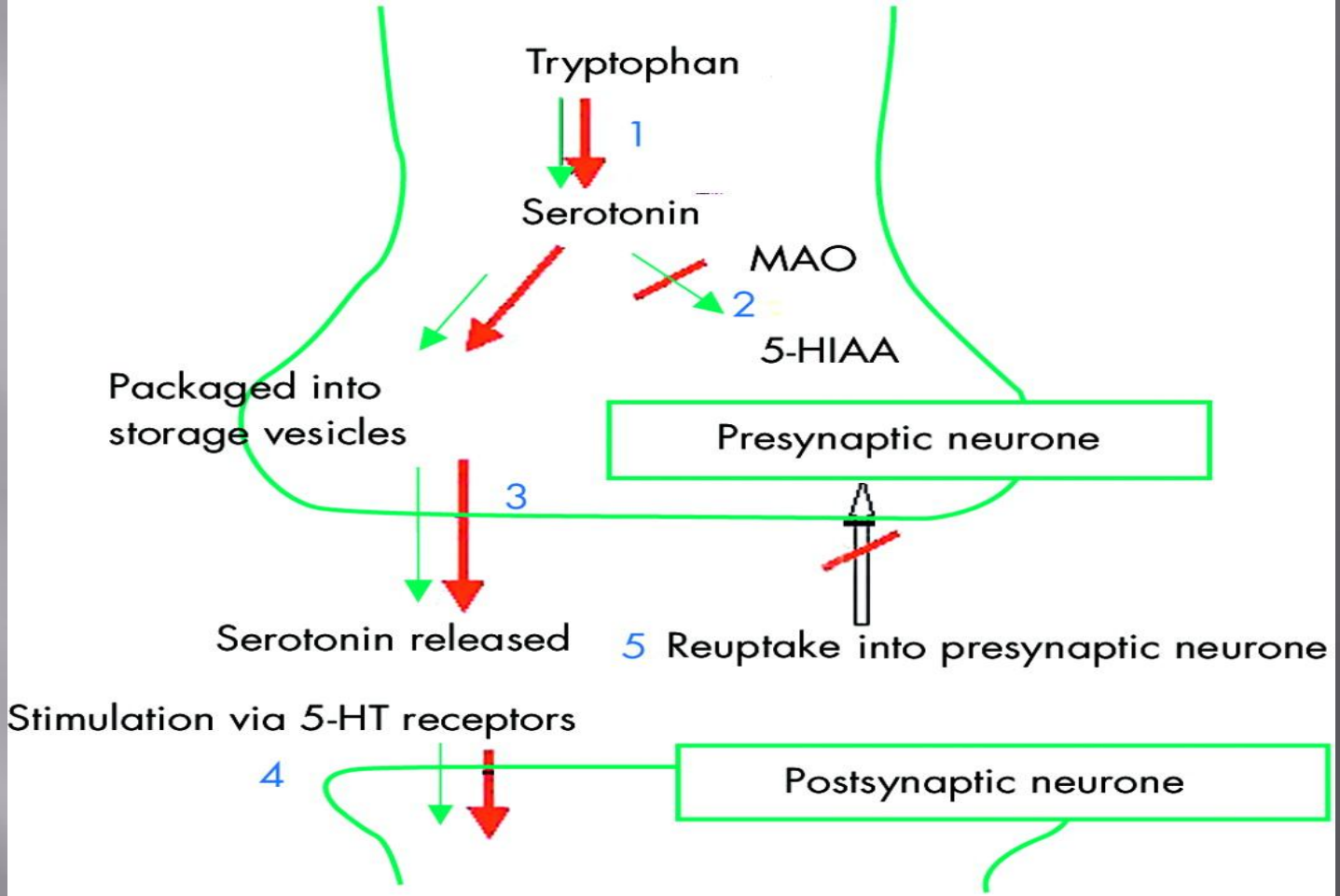

Tryptophan
5-HTP
Serotonin
Transmitting Neuron
Vesicle Containing Serotonin
Serotonin Re-uptake Port
Synapse
Serotonin Receptors
Target Cell

Table 1

Effects of 5-HT receptor subtypes in relation to serotonin toxicity

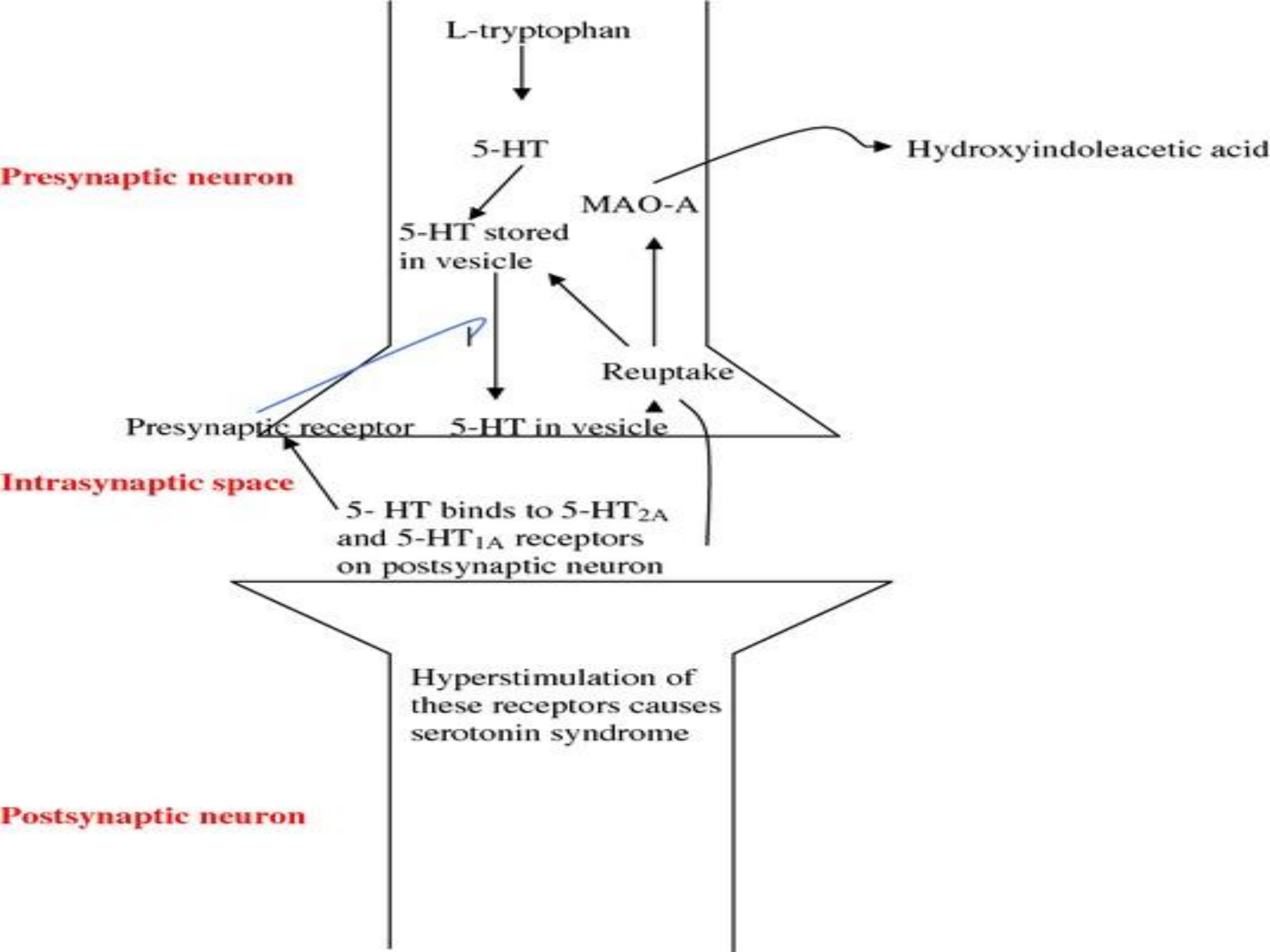
5-HT RECEPTOR	MAIN ACT ION RELATED TO SEROTONIN TOXICITY
5-HT_{1A}	Neuronal inhibition, regulation of sleep, feeding, thermoregulation, hyperactivity associated with anxiety, hypoactivity associated with depression
5-HT_{1D}	Locomotion, muscle tone
5-HT_{2A}	Neuronal excitation, learning, peripheral vasoconstriction, platelet aggregation
5-HT_{2B}	Stomach contraction
5-HT_{3}	Nausea and vomiting, anxiety
5-HT_{4}	Gastrointestinal motility

5- nin.



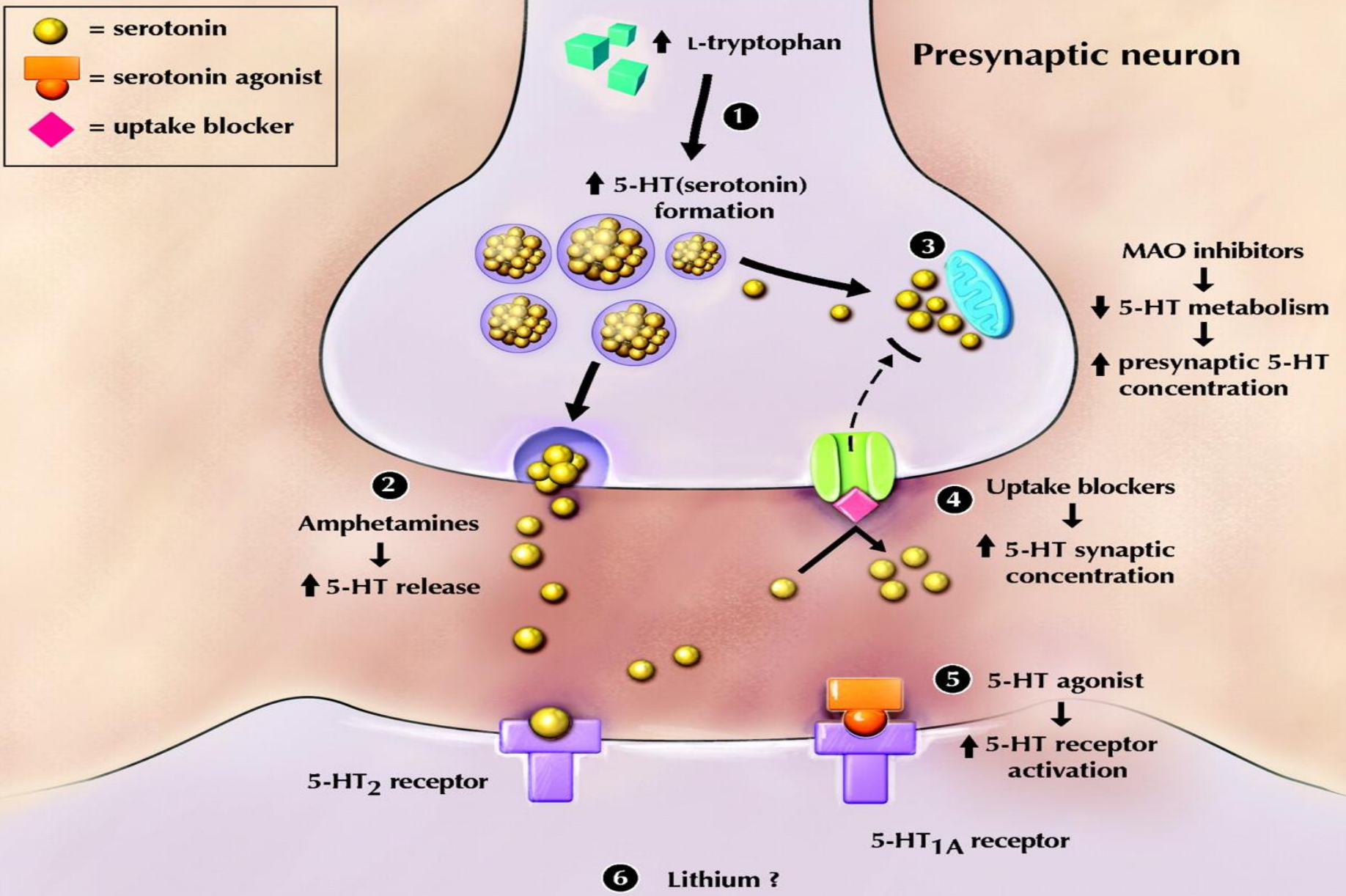
1 Increased substrate
2 Inhibited serotonin metabolism
3 Increased release of serotonin into synaptic cleft
4 Postsynaptic receptor stimulation
5 Inhibited serotonin reuptake

Grosset K A , Grosset D G J Neurol Neurosurg Psychiatry 2004;75:iii2-iii8


L-tryptophan
5-HT
Hydroxyindoleacetic acid
Presynaptic neuron
MAO-A
5-HT stored
in vesicle
Reuptake
Presynaptic receptor
5-HT in vesicle
Intrasynaptic space
5- HT binds to 5-HT2A
and 5-HT1A receptors
on postsynaptic neuron
Hyperstimulation of
these receptors causes
serotonin syndrome
Postsynaptic neuron

Etiology & Pathophysiology

- Serotonin syndrome is the result of overstimulation of 5-HT_{1A} receptors in central grey nuclei and the medulla and, perhaps, of overstimulation of 5-HT_2receptors



Birmes P et al. CMAJ 2003;168:1439-1442

Mechanism	Drug
Metabolic serotonin precursor	L-tryptophan
Inhibit serotonin metabolism	MAOIs
Increase serotonin release	amphetamines
	lithium
	MDMA (Ecstasy)
Inhibit serotonin reuptake	cocaine
	dextromethorphan
	merperidine
	SSRIs
	tricyclic antidepressants
	trazodone
	venlafaxine
serotonin receptor agonists	buspirone
	lysergic acid diethylamide(LSD)
dopamine agonists	l-dopa

Table 1: Situations that cause overstimulation of serotonin ($5\text{-}HT_{1A}$) receptors[2,3,8]

Situation	Associated drugs
Excess of precursors of serotonin or its agonists	Buspirone, L-dopa, lithium, LSD, L-tryptophan, trazodone
Increased release of serotonin	Amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, reserpine
Reduced reuptake of serotonin	SSRI, TCA, trazodone, venlafaxine, meperidine
Slowing down of serotonin metabolism	MAOI, e.g., isocarboxazid, selegiline

Note: LSD = lysergic acid diethylamide, MDMA = methylenedioxy-methamphetamine, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors.

Class	Drugs
Antidepressants	Monoamine oxidase inhibitors (MAOIs),[1] TCAs,[1] SSRIs,[1] SNRIs,[1] bupropion,[6] nefazodone,[7] trazodone[7]
Opioids	tramadol,[1] pethidine,[1] fentanyl,[1] pentazocine,[1] buprenorphine[8] oxycodone,[9] hydrocodone[9]
CNS stimulants	phentermine,[10] diethylpropion,[10] amphetamine,[3][10] sibutramine,[1] methylphenidate,[10] methamphetamine,[11] cocaine[10]
5-HT_1 agonists	triptans[1][10]
Psychedelics	MDMA,[1] MDA,[1] 5-Methoxy-diisopropyltryptamine,[1] LSD[12][13]
Herbs	St John's Wort,[1] Syrian rue,[1] Panax ginseng,[1] Nutmeg,[14] Yohimbe[15]
Others	tryptophan,[1] L-Dopa,[16] valproate,[1] buspirone,[1] lithium,[1] linezolid,[1][17] dextromethorphan,[1] 5-hydroxytryptophan,[7] chlorpheniramine,[10] risperidone,[18] olanzapine,[19] ondansetron,[1] granisetron,[1] metoclopramide,[1] ritonavir[1]

Etiology & Pathophysiology

- Overdosing with single agents such as SSRIs does not often cause severe toxicity.
- Approximately 15% of SSRI overdoses result in moderate symptoms.
- Severe cases appear to be more likely after drug interactions, particularly monoamine oxidase inhibitors (MAOIs) interacting with other antidepressants or with serotonin releasers, such as amphetamines
- Patients who are genetically deficient in the cytochrome P450 2D6 enzyme (8% of whites) are more susceptible if they are taking drugs such as venlafaxine, paroxetine, tricyclics, dextromethorphan, and methadone.

Table 2

Combinations That May Result in Serotonin Syndrome

All SSRIs in combination
Venlafaxine & lithium
Venlafaxine & moclobemide
Venlafaxine & fluoxetine
Venlafaxine & mirtazapine
Fluoxetine & sertraline
Fluoxetine & tramadol
Trazodone & buspirone
Clomipramine & MAOI
Clomipramine & trazodone
Clomipramine & moclobemide
Dextromethorphan & paroxetine
Dextromethorphan & moclobemide
Linezolid & citalopram
SSRI & St. John's wort
SSRI & MAOI
Meperidine & MAOI

SSRI: selective serotonin reuptake inhibitor; MAOI: monoamine oxidase inhibitor.

Source: References 2, 6, 9.

Cognitive-Behavioral	Percent of total cases
confusion/disorientation	54%
agitation/irritability	35%
coma/unresponsive	28%
anxiety	16%
hypomania	15%
lethargy	15%
seizures	14%
insomnia	0%
hallucinations	6%
dizziness	6%
Neuromuscular	
myoclonus	57%
hyperreflexia	55%
muscle rigidity	49%
tremor	49%
ataxia/incoordination	38%
shivering/chills	25%
nystagmus	13%
Babinski's sign (bilateral)	14%
Autonomic Nervous System	
hyperthermia	46%
diaphoresis	46%
sinus tachycardia	41%
hypertension	33%
tachypnea	28%
dilated pupils	26%
non-reactive pupils	18%
flushed skin	14%
hypotension	14%
diarrhea	12%
abdominal cramps	5%
salivation	5%

Table 2

Signs and symptoms of serotonin syndrome

SERIOUSNESS	AUTONOMIC SIGNS	NEUROLOGICAL SIGNS	MENTAL STATUS
Mild	• Afebrile or low-grade fever • Tachycardia • Mydriasis • Diaphoresis or shivering	• Intermittent tremor • Akathisia • Myoclonus • Mild hyperreflexia	• Restlessness • Anxiety
Moderate	• Increased tachycardia • Fever (up to 41°C) • Diarrhea with hyperactive bowel	• Hyperreflexia • Inducible clonus • Ocular clonus (slow continuous lateral eye	• Easily startled • Increased confusion • Agitation and hypervigilance

Diagnosis

- a history of use of a serotonergic agent
- recognized signs and symptoms
- the exclusion of other conditions are required

Diagnosis

- The first criteria that were rigorously evaluated were introduced in 1991 by Harvey Sternbach, a professor of psychiatry at UCLA.
- Researchers in Australia have later developed the Hunter Serotonin Toxicity Criteria, which has better sensitivity and specificity, 84% and respectively 97%.
- **Radomski and colleagues (2000)** have revised these criteria and classified serotonin syndrome as a mild state of serotonin-related symptoms, or serotonin syndrome (full-blown form) (4 major symptoms or 3 major ones plus 2 minor ones) or toxic (coma, generalized tonic-clonic seizures, fever that might exceed 40°C)

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]

Table 4

Decision rules for diagnosing serotonin syndrome in the presence of serotonergic agents within the past 5 weeks: *Hunter serotonin toxicity criteria*.

IN THE PRESENCE OF 1 OR MORE SEROTONERGIC DRUGS (WITHIN THE PAST 5 WEEKS)	YES, THEY HAVE SEROTONIN SYNDROME OR TOXICITY
If patients have spontaneous clonus	Yes
If patients have inducible clonus *and* either agitation *or* diaphoresis	Yes
If patients have ocular clonus *and* agitation *or* diaphoresis	Yes
If patients have tremor *and* hyperreflexia	Yes
If patients are hypertonic *and* have a temperature > 38°C *and* have ocular clonus *or* inducible clonus	Yes

Adapted from Dunkley et al[7] with permission from Oxford University Press.

Laboratory findings

- There is no specific test for serotonin syndrome.
- An elevation of the **total creatine kinase** and **leukocyte count and elevated transaminase levels** or **lower bicarbonate levels** have been reported.

Prognosis

- The mortality of severe serotonin syndrome is estimated to range from **2% to 12%.**
- The Toxic Exposure Surveillance System in the United States reported 93 deaths due to serotonin syndrome in 2002

Differential Dx

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

Differential Dx

Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Mechanism	Serotonin excess	Dopamine antagonism
Onset of Symptoms	Minutes to hours	Days to weeks
Resolution of symptoms	Less than 24 hours	5-14 days
Neuromuscular	Myoclonus, hyperreflexia	"lead pipe" rigidity
Rhabdomyolysis	Rare	Common
Metabolic acidosis	Rare	Common
Elevated transaminases	Rare	Common

Diffential Dx

Table 2: Most frequent distinctions between serotonin syndrome and neuroleptic malignant syndrome[2,3,8–10,17–20]

Characteristic	Serotonin syndrome	NMS
Onset	Sudden, within 24 h following introduction of a serotonergic agent	Slower, within 7 d following introduction of a neuroleptic agent
Symptoms	Agitation, diarrhea	Dysphagia, hypersalivation, incontinence
Signs	Dilated pupils, myoclonus, hyperreflexia	Hyperthermia (> 38ºC), akinesia, extrapyramidal "lead pipe" rigidity, rhabdomyolysis
Mortality	23 deaths reported until 1999*	15%–20%

Note: NMS = neuroleptic malignant syndrome.
*No percentage is reported in the literature, because there are too few cases.

Table 4

Clinical Presentation of Serotonin Syndrome and Differential Diagnosis

Clinical Presentation	Serotonin Syndrome	NMS	Anticholinergic Delirium
Tachycardia	+	+	+
Hypertension	+	+	+
Muscle rigidity	+	+	–
Hyperthermia >41.1°C	+	+	–
Hyperreflexia	+	–	–
Myoclonus	+	–	–
Shivering	+	–	–
Acute onset	–	–	+
Restlessness, confusion, agitation	+	–	+
Bowel sound	+	–	–

NMS: neuroleptic malignant syndrome; +: present; –: not present.
Source: Reference 2.

NMS vs SS

- Patients with NMS are usually akinetic with rigidity, have decreased levels of consciousness, and are more likely to have mutism rather than rambling speech, which is associated with serotonin toxicity.
- The onset of NMS is slow, developing over days rather than hours

Management

- Serotonergic agents must be discontinued
- Supportive therapy
  - control of agitation
  - control of autonomic instability
  - control of hyperthermia
- Additionally, those who ingest large doses serotonergic agents may benefit from gastrointestinal decontamination with activated charcoal if it can be administered **within an hour** of overdose

Management

- intravenous fluids and hydration
- serious myoclonus and hyperreflexia, are sometimes treated with benzodiazepines, but there is little evidence for this approach.
- Hyperthermia should be aggressively managed with external cooling, hydration.
- Patients with a temperature higher than 41°C should be intubated with induced neuromuscular paralysis.

Management

- There is a **limited role for traditional antipyretics**, as the mechanism of serotonin syndrome is due to muscle tone rather than central thermoregulation.
- Physical restraints should be avoided, as they can increase hyperthermia, lactic acidosis, and rhabdomyolysis.

Management

- The antihistamine *cyproheptadine*, which is also a 5-HT_{2A} inhibitor, should be considered in moderate cases and is recommended in severe cases.
- It is available only as an oral preparation; the initial dose is 12 mg; the dosage is then adjusted to 2 mg every 2 hours until symptoms improve

Management

- Some antipsychotics have 5-HT_{2A} antagonist effects and are sometimes used and *olanzapine* and intramuscular *chlorpromazine* (50 to 100 mg) are options (Chlorpromazine can cause serious hypotension and should be avoided in severe cases with shock)
- Caution is required in using antipsychotics for treating serotonin syndrome, as **NMS can be misdiagnosed as serotonin syndrome**

Management

- ***Dantrolene,*** a skeletal muscle relaxant used for treatment of NMS, has been reported to improve symptoms of serotonin syndrome in a case series however, it has also been implicated in the development of serotonin toxicity and is **not generally recommended**
- ***Propranolol,*** which has 5-HT_{1A} antagonist activity and a long half-life, can potentiate hypotension and make improvement in tachycardia a less effective strategy for monitoring response to treatment

Key points

- Serotonin syndrome is not an idiosyncratic drug reaction, but a **predictable response to elevated serotonin levels.** Medications that affect any of the steps in serotonin metabolism or regulation can provoke toxicity.
- **Antidepressants** are frequently implicated in serotonin syndrome. Interactions with other medications, such as common over-the-counter products (eg, dextromethorphan), can cause serious toxicity.

Key points

- Symptoms can occur **within 6 to 8 hours** of initiating or increasing the dosage of serotonergic medications. Drugs with long half-lives can interact several weeks after discontinuation.
- Treatment is based on the severity of the presentation. Many cases will be self-limited if the medications are stopped.

A notable case

- The most widely recognized example of serotonin syndrome was the death of Libby Zion in 1984.
- Libby was a freshman at Bennington College in Vermont at her death on March 5, 1984, at age 18.
- She died within 8 hours of her emergency admission to the New York Hospital Cornell Medical Center.

A notable case

- She had an ongoing history of depression, and came to the Manhattan hospital on the evening of March 4, 1984, with a fever, agitation and "strange jerking motions" of her body. She also seemed disoriented at times. The emergency room physicians were unable to diagnose her condition definitively, but admitted her for hydration and observation. Her death was caused by a combination of meperidine (Demerol) and phenelzine.

A notable case

- The doctor who prescribed the Demerol was a medical intern (PGY1) who was in charge of 40 patients that night.
- The case had an impact on graduate medical education and residency work hours.
- **New York State Department of Health Code**, Section 405, also known as the **Libby Zion law**, is a regulation that limits the amount of resident physicians' work in New York State hospitals to roughly **80 hours per week**
- In July 2003, ACGME adopted similar regulations for all accredited medical training institutions in the United States

Questions

All of the following may precipitate serotonin syndrome except:

a. Paroxetine
b. Meperidine
c. Fentanyl
d. Tramadol
e. Dextromethorphan

Questions

All of the following are included in the serotonin syndrome triad except:

a. Hepatic dysfunction
b. Cognitive dysfunction
c. Autonomic dysfunction
d. Neuromuscular dysfunction

Questions

Serotonin syndrome may present like all of the following except:

a. Sympathomimetic syndrome
b. Neuroleptic malignant syndrome
c. Acute psychosis
d. Rhabdomyolysis
e. Acute unilateral stroke

Case example

34-year-old, 86-kg, married white woman presented to our academic emergency department with symptoms of confusion, agitation, and rigor at 03:00 am. Her husband found her at home lying on the floor about 02:30 am. He figured out that 13 tablets of 20-mg ***paroxetine (Paxil®)*** and 15 tablets of 300-mg ***moclobemide (Aurorix®)*** were missing. He did not come across any other drug or alcohol at home. The patient had no prior medications, and there was nothing significant in her medical and family history. Vital signs at presentation were as follows: 140/80 mmHg blood pressure, 100 beats/min pulse rate, 20 breaths/min respiratory rate, 38.3°C temperature, and 90% oxygen saturation. She was drowsy, disoriented, non-cooperative, sweating, and had a Glasgow Coma Score of 10 (E2M5V3)

- She had rapid but decreased depth of respiratory effort. Half-dilated pupils were isochoric and bilateral wandering horizontal eye movements called as "ping-pong gaze" was observed. There was muscle rigidity all over the body especially in the lower extremities. In addition, hyper-reflexia was found in deep tendon reflexes bilaterally both in the lower and upper extremities. No trauma evidence was examined and rest of the examination was unremarkable. Her capillary glucose level was 167 mg/dl. Electrocardiogram showed no evidence of arrhythmia or conduction defect but sinus tachycardia . Arterial-blood-gas (ABG) result at presentation was as follows: 7.051 pH, 52 mmHg pO2, 74.7 mmHg pCO2, 15% HCO3, and 77% SaO2, which showed metabolic acidosis. Complete blood count, electrolytes, liver, and renal function tests, urine pregnancy test, urine toxicology screen (amphetamine, benzodiazepine, opiate, barbiturate, cocaine, and phencyclidine), and brain computerized tomography were normal. Supplemental oxygen was given at 4 l/min via simple facemask.

- She was admitted to the medical intensive care unit of the emergency department, placed on a cardiac monitor, intravenous line and normal saline started, orogastric catheter was placed, and gastric lavage was done. After gastric lavage, 1 g/kg activated charcoal was passed down the orogastric tube. Approximately in 1 h diffused continuous muscle hyperactivity (myoclonus, tremor, and rigidity) was started. Although a total of 8 mg ***midazolam*** was given intravenously, it lasted almost 20 min. The patient began shivering severely and vital signs began to deteriorate further. We decided to intubate and paralyze her to control the airway and avoid further muscle hyperactivity and rhabdomyolysis, as she had low SaO2 despite supplemental oxygen (70-80%), hyperthermia (max. 42.3ºC), hypercarbia (102-145 mmHg), and uncontrolled persistent muscle rigidity and shivering.

- Just before intubation ABG was at 6.852 pH, 74.7 mmHg pO2, 37 mmHg pCO2, 21% HCO3, and 73% SaO2. While she was intubated, paralysis was achieved with continuous infusion of ***vecuronium*** and sedation with intermittent doses of ***midazolam***. Even necessary supportive care (mechanical ventilation, buffer replacement, etc.), ***cyproheptadine (Periactin®),*** a nonspecific serotonergic antagonist, 4 mg every 4 h via orogastric tube and ***dantrolene***, a nonspecific muscle relaxant, 100 mg qid intravenously was given soon after consultation with a medical toxicologist. About 20 h after ED presentation the patient suffered cardiopulmonary arrest probably because of multiple organ failure and deep metabolic acidosis. Toxicology results revealed that blood levels of ***moclobemide and paroxetine*** were 26.53 and 3.09 mg/l, respectively. In addition, autopsy findings were unremarkable and support the diagnosis of serotonin syndrome as the cause of demise.

THE END

Thank you !