Serotonin Syndrome

從 Libby Zion 與「美國住院醫師工時設限」說起…

新光急診 張志華

103.07.02

N Engl J Med 2005;352:1112-20
http://en.wikipedia.org/wiki/Libby_Zion_law

Libby Zion – history

- 促成美國對住院醫師的工時設限〔每週低於80小時〕的主要原因，是因兩位急診的住院醫師〔PGY-1和PGY-2〕因過勞而開給病人〔Libby Zion〕不該開的藥，導致病人不幸因此死亡

Libby Zion – the patient

- Libby是大學新生，因不適就醫，剛被送入急診時就出現 strange jerking motions
- 有可能是 serotonin syndrome 的初期表現，因她原來就服用抗憂鬱劑phenelzine
- 過勞的PGY住院醫師〔同時照顧40個病人〕卻開立了meperidine來治療病人的症狀，而導致病情加重 - 躁動並燒到42度C，進而心臟停止

Libby Zion Law

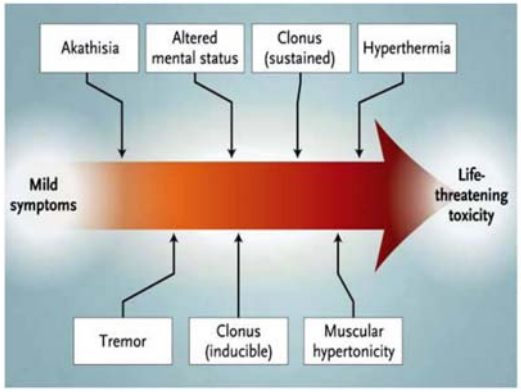
- Libby發生serotonin syndrome後，高燒躁動，護士call醫生，醫生忙不過來只電話order要約束病人及打Haldol治療，沒去診視病人，後來燒太高就cardiac arrest了
- 病人Libby死後，她當律師兼報紙專欄作者的爸爸就提告，訴訟了十幾年，最後醫師敗訴〔民事〕，不久後就有了Libby Zion Law

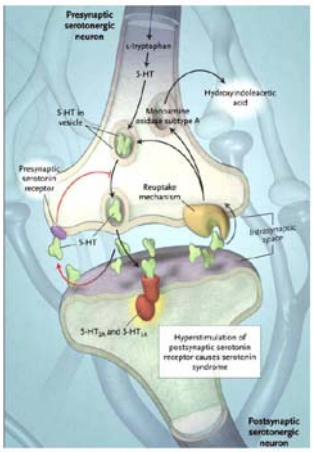
Definition

- Clinical triad:
  1. Mental-status changes
  2. Autonomic hyperactivity
  3. Neuromuscular abnormalities

Epidemiology

- > 85% of physicians are unaware of SS as a clinical diagnosis
- SS occurs in 14~16% of persons who overdose on SSRIs





Serotonin Biosynthesis and Metabolism

Drugs associated with SS

- **Selective serotonin-reuptake inhibitors (SSRI):**
  - **sertraline**, **fluoxetine**, **fluvoxamine**, paroxetine, and citalopram
- **Antidepressant drugs:**
  - trazodone, nefazodone, buspirone, clomipramine, and venlafaxine, **imipramine**
- **Monoamine oxidase inhibitors (MAOI):**
  - **phenelzine**, moclobemide, clorgiline, and isocarboxazid
- **Anticonvulsants:**
  - **Valproate**

Drugs associated with SS

- **Analgesics:**
  - **meperidine**, **fentanyl**, **tramadol**, and pentazocine
- **Antiemetic agents:**
  - **ondansetron**, granisetron, and **metoclopramide**
- **Antimigraine drugs:**
  - **sumatriptan**
- **Bariatric medications:**
  - Sibutramine
- **Lithium**

Drugs associated with SS

- **Antibiotics:**
  - **linezolid** and ritonavir
- **OTC cough and cold remedies:**
  - **dextromethorphan**
- **Drugs of abuse:**
  - **MDMA**, or "ecstasy", LSD, **amphetamines**, **cocaine**, 5-methoxy-diisopropyl-tryptamine, Syrian rue
- **Dietary supplements and herbal products:**
  - tryptophan, Hypericum perforatum (St. John's wort), Panax **ginseng**

Drugs associated with SS

- **Zoloft**, **Prozac**, Sarafem, **Luvox**, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, **Nardil**, Manerix, Marplan, **Depakene**, **Demerol**, **Duragesic**, Sublimaze, Ultram, Talwin, **Zofran**, Kytril, Reglan, **Primperan**, Imitrex, Meridia, Redux, Pondimin, **Zyvox**, Norvir, Parnate, **Tofranil**, Remeron

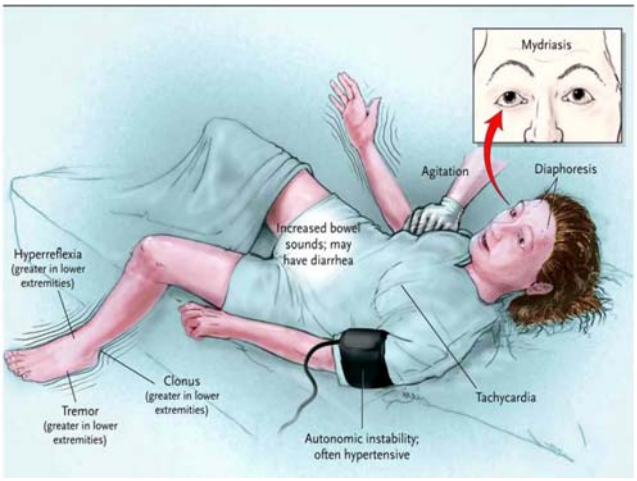
Drugs associated with severe SS

- ***Phenelzine*** and ***meperidine***
- Tranylcypromine and imipramine
- Phenelzine and selective serotonin-reuptake inhibitors
- Paroxetine and buspirone
- Linezolid and citalopram
- Moclobemide and selective serotonin-reuptake inhibitors
- Tramadol, venlafaxine, and mirtazapine

Serotoninergic Drugs	
Antidepressants	
Monoamine oxidase inhibitors: phenelzine, tranylcypromine, isocarboxazid, pargyline, rasagiline, and selegiline	
Selective serotonin reuptake inhibitors: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram	
Serotonin/norepinephrine reuptake inhibitors: venlafaxine, desvenlafaxine, and duloxetine	
Cyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine	
Miscellaneous: trazodone (moderate potency), bupropion (low potency)	
Other Agents	
Amantadine (low potency)	L-tryptophan and 5-hydroxytryptophan (high potency)
Amphetamines (moderate potency)	Lysergic acid diethylamide (moderate potency)
Bromocriptine (low potency)	
Buspirone (moderate potency)	Meperidine (high potency)
Carbamazepine (low potency)	Mescaline (moderate potency)
Cocaine (moderate potency)	Metoclopramide (low potency)
Codeine (low potency)	Pentazocine (low potency)
Dextromethorphan (high potency)	Pergolide (low potency)
	Reserpine (low potency)
Fentanyl (moderate potency)	St. John's wort (moderate potency)
Levodopa (moderate potency)	Sumatriptan and related triptans (high potency)
Linezolid (high potency)	
Lithium (high potency)	Tramadol (high potency)

Manifestations

- Mental-status changes
  - ***Agitation*** and delirium
- Autonomic hyperactivity
  - Tachycardia on admission, mydriasis, ***diaphoresis***, and the presence of bowel sounds and diarrhea
- Neuromuscular abnormalities
  - Hyperreflexia, inducible clonus, ***myoclonus***, ocular clonus, spontaneous clonus, peripheral hypertonicity, and shivering



Serotonin syndrome

- Rapid onset
  - Within minutes after a change in medication or self-poisoning
  - 60% present within 6h after initial use of medication, an overdose, or a change in dosing

Severe serotonin syndrome

- Severe hypertension
- Severe tachycardia
- Core temperature > 41.1˚C.
- Metabolic acidosis
- Rhabdomyolysis
- Elevated levels of serum aminotransferase
- Seizures
- Renal failure
- DIC (disseminated intravascular coagulopathy)

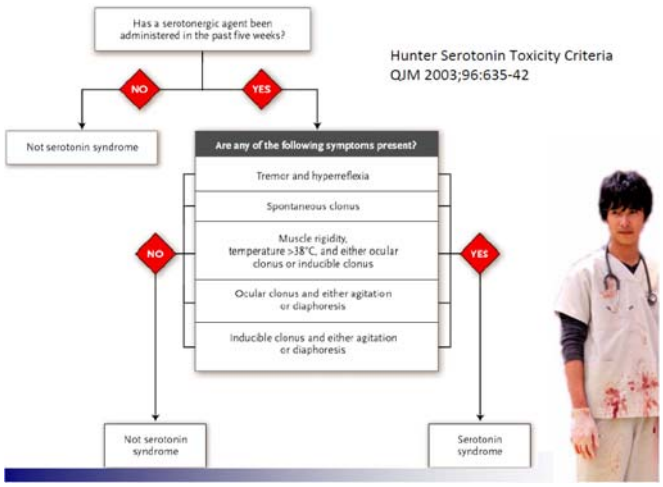
Many abnormalities are due to poorly treated hyperthermia

Diagnosis - presentation

- Key findings:
  - Tremor
  - Clonus / myoclonus
  - Akathisia
- No EPS

Diagnosis - PE

- Increased DTR
- Inducible clonus
- Muscle rigidity
- Mydriasis (dilated pupils)
- Sialorrhea
- Increased bowel sounds (diarrhea)
- Pallor
- Diaphoresis



Hunter Serotonin Toxicity Criteria
QJM 2003;96:635-42

Clinical Presentation of Serotonin Syndrome					
Cognition-Behavior	**%**	**Autonomic Dysfunction**	**%**	**Neuromuscular Dysfunction**	**%**
Confusion/disorientation	54	Hyperthermia	46	Myoclonus	57
Agitation	35	Diaphoresis	46	Hyperreflexia	55
Coma	28	Sinus tachycardia	41	Muscle rigidity	49
Anxiety	16	Hypertension	33	Tremor	49
Hypomania	15	Tachypnea	28	Hyperactivity	43
Lethargy	15	Dilated pupils	26	Ataxia	38
Seizures	14	Unreactive pupils	18	Shivering	25
Insomnia	10	Flushed skin	14	Babinski sign	14
Hallucinations	6	Hypotension	14	Nystagmus	13
Dizziness	6	Diarrhea	12	Teeth chattering	6
		Abdominal cramps	5	Opisthotonus	6
		Salivation	5	Trismus	6

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 (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 / absent	Normal / 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

Management

- Removal of the precipitating drugs
- Supportive care
- Control of agitation
- Control of autonomic instability
- Control of hyperthermia
- 5-HT_{2a} antagonists

Mild cases

- Mild cases: hyperreflexia and tremor but no fever
- Treatment
  - Supportive care
  - Removal of the precipitating drugs
  - Benzodiazepines (BZD)
- Typically resolve within 24 hours

Moderate cases

- Supportive treatment
- BZD
- Cooling
- 5-HT2a antagonists

Severe cases

- Hyperthermic (> 41.1°C)
  - Immediate sedation
  - Neuromuscular paralysis
  - Orotracheal intubation

Agitation control

- Benzodiazepines [O]
  - Essential regardless of SS severity
- Physical restraints [X]
  - Mortality ↑ - isometric contractions
  - Severe lactic acidosis, hyperthermia, rhabdomyolysis
- Propofol [O]

5-HT2a Antagonists

- **Cyproheptadine (Periactin)**
  - Initial dose: po 12 mg and then 2 mg q2h if symptoms continue
  - Maintenance dose: po 8 mg q6h
- **Olanzapine ?**
  - Sublingual 10 mg
- **Chlorpromazine ?**
  - Intramuscular 50-100 mg

BP control

- Hypertension and tachycardia
  - Short-acting agents such as nitroprusside and esmolol
- Hypotension
  - Direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, and epinephrine)

Temperature control

- Hyperthermia (>41.1°C)
  - Immediate paralysis (vecuronium)
  - Orotracheal intubation and ventilation
- Avoid succinylcholine
  - Risk of arrhythmia from hyperkalemia associated with rhabdomyolysis

Other treatment

- Antipyretic agents [X]
- Propranolol [X]
- Bromocriptine [X]
- Dantrolene [X]

Prognosis

- Mortality: 11%
- Poorly treated hyperthermia leads to morbidity and mortality

Take home message

1. Clinical triad
   - Mental-status changes
   - Autonomic hyperactivity
   - Neuromuscular abnormalities
2. Treatment
   - Agitation
   - Temperature
   - Antidotes

Take home message

1. Clinical triad
   - Mental-status changes - ***agitation***
   - Autonomic hyperactivity - ***diaphoresis***
   - Neuromuscular abnormalities - ***myoclonus***
2. Treatment
   - Agitation - ***BZD***
   - Temperature - ***cooling***, ***vecuronium***
   - Antidotes - ***cyproheptadine***

Thank You