



# Serotonin Syndrome: An Update

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# Acknowledgements

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# Objectives

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- Brief review of serotonin syndrome
- Why is it important?
- Causative agents
- What does it mean for medication safety?



# Definition

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- Excessive serotonergic activity in the central and peripheral nervous systems
- Specifically at 5-HT<sub>2a</sub> receptors

■ (Sun-Edelstein et al 2008; Ables & Nagubilli 2010)



# The Triad of Serotonin Syndrome

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- Mental state changes
- Autonomic hyperactivity
- Neuromuscular abnormalities
  
- Other features



# Mild Serotonin Syndrome

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- Confusion, agitation
- Tachycardia, diaphoresis, tachycardia, low grade fever
- Inducible clonus (dorsiflexion of ankle), tremor, hyperreflexia (particularly lower limbs)

■ (Boyer and Shannon 2005; Sun-Edelstein et al 2008)



# Moderate Serotonin Syndrome

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- Symptoms of mild PLUS
- Easily startled
- Fever (less than 41°C), diarrhoea
- Inducible or ocular (rapid equal lateral movements, different from nystagmus)  
clonus

■ (Boyer and Shannon 2005)



# Severe Serotonin Syndrome

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- Symptoms of moderate PLUS
- Delirium, coma
- Fever (more than 41°C)
- Increased muscle tone, spontaneous clonus

■ (Boyer and Shannon 2005)



# Other features

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- Seizures
- Rhabdomyolysis
- Renal failure
- Cardiac arrhythmias
- DIC
- Death

■ (Boyer and Shannon 2005)



# Epidemiology

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- Prevalence
  - Up to 15% of overdoses have moderate symptoms
- Fatalities
  - 2-12%

■ (Sun-Edelstein et al 2008; Frank 2008)



# Pathophysiology

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- Overstimulation of the serotonin system
- Predictable on a synapse level
- Some prefer “serotonin toxicity”
- Argue it's not idiosyncratic like neuroleptic malignant syndrome



# Is it predictable

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- Who?
  - What context?
  - What dosage of medications?
  - What combination of medications?
  - When?
- 
- I would argue that it is very hard to predict



# Diagnosis: Sternbach (1991)

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- Recent addition or increase in a known serotonergic agent
- Absence of other possible aetiologies (infectious, metabolic, substance abuse or withdrawal, etc).
- No recent addition or increase in a neuroleptic agent prior to the onset of the above features.
- At least three of the following clinical features
  - Mental status changes (confusion, hypomania)
  - Agitation
  - Myoclonus
  - Hyperreflexia
  - Diaphoresis
  - Shivering
  - Tremor
  - Diarrhoea
  - Incoordination
  - Fever



# Diagnosis: Hunter (2003)

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- In the presence of a serotonergic agent:
  - Spontaneous clonus
  - Inducible clonus OR ocular clonus AND agitation OR diaphoresis
  - Inducible clonus OR ocular clonus AND hypertonicity AND temperature  $> 38^{\circ}\text{C}$
  - Tremor AND hyperreflexia



# Any dose can cause serotonin syndrome

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- First dose of citalopram 20mg
- Duloxetine 60mg
- Duloxetine 30mg

- (Turedi et al 2007; Hadikusumo et al 2009; Liu et al 2009)



# Large doses by antidepressants alone can be fatal

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- 55 year old man
- 180 slow release paroxetine 25mg
- Unknown amount of regular paroxetine
- ICU and period of intubation
- Died of pulmonary embolus on Day 9

■ (Muzyk et al 2010)



# A + B + C + D

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- Multiple pro-serotonergic agents
- Elderly patient
  - Venlafaxine, mirtazapine, quetiapine
    - (Poeschla et al 2011)
- Surgical patient
  - Duloxetine, lithium, quetiapine, fentanyl, ondansetron
    - (Altman et al 2010)



# Common things- commonly

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- Tramadol
  - (Tashakori and Afshari 2010)
- Fentanyl patch and intravenous
  - (Kirschner and Donovan 2008)
- Dextromorphan
  - (Navarro et al 2006; Schwartz et al 2008)



# Out of the blue

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- First report 2003
- Post elective parathyroidectomy
- Serious delirium with no cause
- Trickle of cases in various journals
- Intravenous methylene blue
- Old drug thought to be safe
- Used to identify the parathyroids



# Out of the blue

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- Seven cases by 2008 including one in Auckland
- All cases had SSRI in background
- Could it be serotonin syndrome?
- Challenges
  - Incomplete descriptions
  - Atypical presentations
    - (Ng et al 2008)



# Out of the blue

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- Increasing number of cases
- Two operative audits of encephalopathy only on antidepressants
- Methylene blue was a powerful monoamine oxidase inhibitor
- Lessons learnt

■ (Ng et al 2010)



# Ecstasy- party on!

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- MDMA (N-methyl-3,4,-methylenedioxymethamphetamine)
  - Most "E"s have 80-150mg MDMA
  - Other drugs
  - Facilitate serotonin release
  - CYP450 2D6 inhibitor
  - Inhibit serotonin reuptake
- (Oesterheld et al 2004; Silins et al 2007)



# Ecstasy- party on!

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- High risk
  - Fatal reports
  - MAOIs (eg phenelzine)
  - RIMAs (eg moclobemide)
  - Not necessarily prescription medication
    - Contaminant or enhancer
      - (Vuori et al 2003)
      - (Silins et al 2007)



# Ecstasy- party on!

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- Less risk
  - SSRIs and SNRIs
  - TCAs
  - Opioids (eg tramadol)
- Intermediate risk
  - Amphetamines
  - Cocaine

■ (Silins et al 2007)

# Scaremongering or weak signal?



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- Triptans (eg sumatriptan)
- Treatment of migraines
- FDA warning (2006)
  - Serotonin syndrome with SSRIs/SNRIs
  - 29 cases
- Soldin et al (2008)
  - 11 cases with triptans alone
- (Evans et al 2010)



# Scaremongering or weak signal?

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- Forty cases in the literature
  - Some were not serotonin syndrome
  - Some fulfilled Sternbach Criteria only
  - Some did not completely exclude other diagnoses
  - Some had inadequate information
- Not enough evidence to suggest a link
  - (Gillman 2010; Evans et al 2010)



# What does this mean for safe prescribing?

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- Hard to predict
- Awareness
- Vigilance
- Listen to patient complaints seriously
- Always consider the diagnosis



# What does this mean for safe prescribing?

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- Thorough examination
- Appropriate details
- Use of criteria
- Adverse reporting



# What does this mean for safe prescribing?

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- Publication
- Education
  - Across professions
  - Between specialties
  - Drug interaction software

■ (Ables & Nagubilli 2010)

Thank you

