Staying out of Trouble: Avoiding Neuroleptic Malignant Syndrome and Serotonin Syndrome

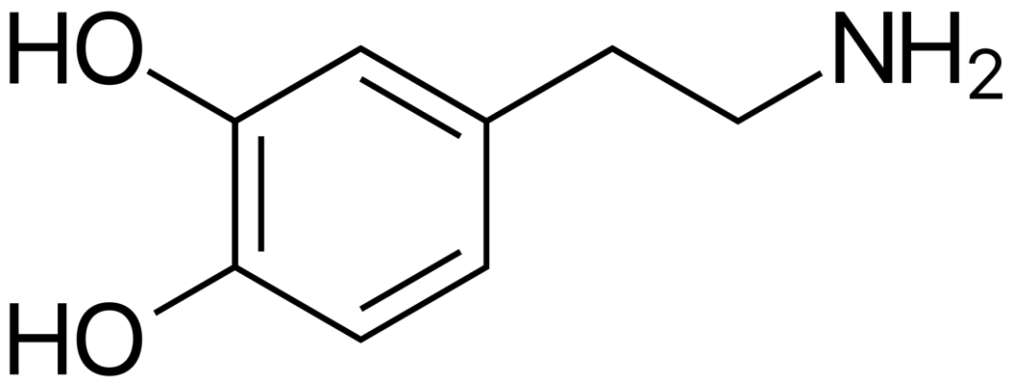
Declaration – pertinent to this talk

- In past years I have participated in clinical trials conducted by Janssen Pharmaceutica
- I recently worked on a publication with support from Janssen Pharmaceutica (described in this talk)
- I have recently been on an advisory board for Janssen Pharmaceutica

Learning Objectives

- Understand the similarities and differences between neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS)
- Be familiar with the Hunter Serotonin Toxicity Criteria
- Know how to limit the risks of patients developing NMS and SS

Dopamine



- First synthesized in 1910
- First identified in human brain in 1957
- Swedish researchers including Carlsson and Hillarp established role as neuro-transmitter in 1958 (Nobel Prize 2000)

Neuroleptic Malignant Syndrome

- Our collective experience
  - Audience's experience
  - My first case
  - Other serious case in Kingston after FG LAI
- My second case

NMS Case Report – Context and Patient

- Double-blind clinical trial comparing risperidone Consta with paliperidone palmitate
- 55 Y.O.W.M. with diagnosis of schizophrenia since age 17
- 4 prior hospitalizations
- Smoker; no alcohol or other substance misuse
- Overweight (BMI 25.7); gum disease and caries; reduced hearing on left side and cerumen in both external ear canals
- Rx prior to study: flupenthixol decanoate 15 mg q 2 weeks X 6 years

NMS Case Report – Treatment in Clinical Trial

- Fluanxol discontinued 22 days prior to randomization
- Day -6 to -3, given paliperidone extended release 3 mg/d for oral tolerability testing
- Paliperidone plasma level undetectable on Day 1 before administration of paliperidone palmitate. Adherence?
- Days 1 and 8 received paliperidone palmitate 50 mg eq in gluteal muscle

NMS Case Report – Development of Syndrome

- Day 15, patient hospitalized
- Confused
- Fever 38.8 deg C (102 deg F)
- Little rigidity but “trouble relaxing muscles”

NMS Case Report – Initial Laboratory Tests

- CK 5,824 (normal 55-197) U/L
- AST 128 (normal 12-45) U/L
- ALT 91 (normal 7-40) U/L
- Other investigations normal including WBC and CXR

NMS Case Report – Treatment of NMS

- Day 16-17 – lorazepam 0.5-1.0 mg/d
- Day 16-21 – ciprofloxacin 500 mg bid given for suspected infection that was later ruled out
- Paliperidone palmitate not given again after Day 8
- Days 19-26 – benztropine 1-2 mg/d
- Day 19 – Patient withdrawn from study after development of serious treatment-emergent side effect of NMS
- Days 27-28 – dose of benztropine tapered and D/C
- Pyrexia treated with acetaminophen as needed

NMS Case Report – Further Developments

- Day 20 – CK 860; AST 49; ALT 52 U/L
- Day 23 – flupenthixol decanoate 15 mg IM q 2 weeks resumed
- Day 28 – patient went on LOA
- Day 34 – patient readmitted, disoriented and feeling unwell. Temperature 38.5 deg Celsius, which soon returned to normal. Weather had been very hot and patient's residence did not have A/C
- Day 36 – patient went on second LOA after investigations all normal
- Day 46 – patient discharged

Janssen Database for PP1M and PP3M

- Includes clinical trials phases 1-3
- 5,008 patients received one or more doses of paliperidone palmitate, 1-monthly or 3-monthly
- Preferred terms from Medical Directory for Regulatory Activities (MedRA, version 16.0) identified patients for case review
- Patients had one or more of the selected terms

List of Preferred Terms Used in the Search for NMS in the Janssen Clinical Trial Database

Hyperthermia malignant	Delirium
NMS	Depressed level of consciousness
Serotonin syndrome	Disorientation
Body temperature increased	Extrapyramidal disorder
Hyperpyrexia	Heart rate abnormal
Pyrexia	Heart rate increased
Catatonia	Hyperhidrosis
Dyskinesia	Hypertension
Dystonia	Hypotension
Freezing phenomenon	Labile blood pressure
Hyperkinesia	Labile hypertension
Hypertonia	Leukocytosis
Muscle necrosis	Loss of consciousness
Muscle rigidity	Muscle enzyme increased
Oculogyric crisis	Myoclonus
Oculogyration	Myoglobin blood increased
Opisthotonus	Myoglobin blood present
Rhabdomyolysis	Myoglobin urine present
Altered state of consciousness	Myoglobinemia
Autonomic nervous system imbalance	Myoglobinuria
Blood creatine phosphokinase abnormal	Parkinsonian crisis
Blood creatine phosphokinase increased	Parkinsonian rest tremor
Blood creatine phosphokinase MM increased	Parkinsonism
Blood pressure abnormal	Parkinson's disease
Blood pressure decreased	Stupor
Blood pressure fluctuation	Tachycardia
Blood pressure increased	Tremor
Cardiovascular insufficiency	Unresponsive to stimuli
Coma	White blood cell count abnormal
Confusional state	White blood cell count increased
Consciousness fluctuating	

Preferred terms used were from Medical Dictionary for Regulatory Activities (MedDRA, version 16.0).

Janssen Database for PP1M and PP3M

- Each identified case reviewed for:
  - Treatment emergent side effects
  - Vital signs
  - Physical examination
  - Laboratory findings
  - Clinical management of the event

Janssen Database for PP1M and PP3M

- One case identified
- 5,008 patients treated for 2,271.6 patient-years
- Raw incidence 0.020% (95% CI between 0.0028% and 0.14%)
- Incidence rate 0.044% (95% CI between 0.042% and 0.13% per year)

Reference

- Low Incidence of Neuroleptic Malignant Syndrome Associated With Paliperidone Palmitate Long-Acting Injectable; A Database Report and Case Study. Kane JM, et al.J Clin Psychopharmacol. 2019 Mar-Apr; 39(2): 180–182

Conclusions from single case in Janssen database

- One case identified
- Patient sensitive to neuroleptic dose, with low dose of flupenthixol for many years
- Both flupenthixol and paliperidone contributed to the development of NMS
- NMS was mild and successfully treated in spite of LAI preparation having been used
- NB that all patients had previously received neuroleptics, at least oral testing dose, so not naive

DSM-5 Diagnosis of NMS

- HETEROGENOUS PRESENTATION
- Hyperthermia over 38 degrees Celsius on at least 2 occasions (oral)
- Diaphoresis
- Generalized rigidity
- CK over 4X ULN
- Changes in mental status
- Autonomic activation and instability
- Rate with SGA 0.01%-0.02%

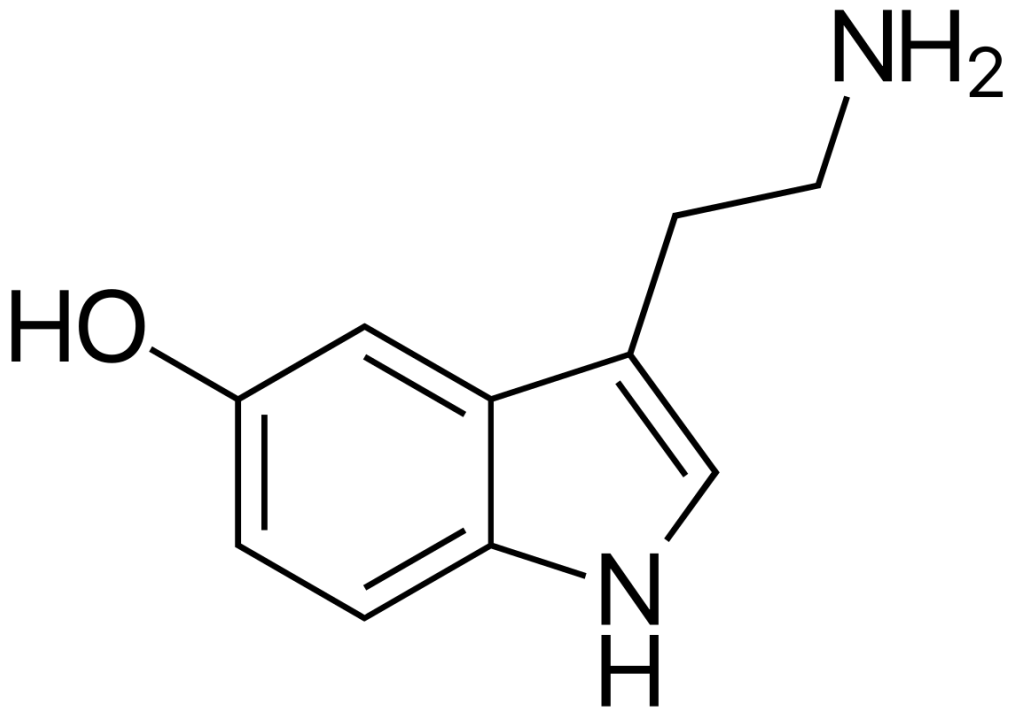
Prevention of NMS

- Prevention
  - Low doses to start with
  - Second generation antipsychotics
  - Care with withdrawal of antiparkinsonian agents
  - Care in replacing low potency FGA
  - Oral test dose before LAI
- Early recognition – be aware of signs
- Risk factors include dehydration, agitation, males

Treatment of NMS

- Cessation of dopamine antagonists or resumption of antiparkinsonians
- General supportive measures, cooling, hydration, etc.
- Ventilatory support if needed
- Dopamine agonists, anticholinergics, BZDZ, dantrolene
- Dialysis if needed
- Can resume neuroleptics after resolution of NMS; second generation antipsychotic meds less risky

Serotonin (5-HT)



- Discovered in 1948
- Discovered in nervous system in 1953
- L-tryptophan in diet
- 5-OH tryptophan crosses BBB
- Decarboxylated to 5-HT
- 5-HT degraded by MAO to 5-HIAA

Serotonin Syndrome

- Our collective experience

Serotonin Toxicity

- First noted by Oates and Sjostrand (1960) in patients who received tryptophan while on therapy with MAOIs
- Insel et al reported “Possible Development of the Serotonin Syndrome in Man” (1982) in patients on MAOI + TCA
- Case of Libby Zion (1984)

Serotonin Syndrome – Libby Zion

- Case of Libby Zion
  - Died age 18 in NYC
  - First year at university
  - Had been treated with phenelzine
  - “Flu-like” illness for a few days
  - Manifested “strange jerking movements” on admission
  - Overworked house staff

Serotonin Syndrome – Libby Zion

- Case of Libby Zion
  - Given meperidine (SSRI opioid)
  - Became more agitated
  - Restrained, haloperidol
  - Temperature reached 107 deg F. the next morning
  - Cardiac arrest

Serotonin Syndrome – Libby Zion

- Consequences of death of Libby Zion
  - House staff in USA limited to 80 h/wk
  - Further understanding of serotonin syndrome
  - Had not been generally known that meperidine could have this interaction with MAOI
  - There are “Drug Error Attorneys” in USA that are experts in this area!

Clonus

- https://www.youtube.com/watch?v=UX75k8s5QUE

Sternbach Criteria for Serotonin Syndrome

- Sternbach (1991) reviewed 38 cases from 10 case reports and 2 case series, and derived diagnostic criteria for Serotonin Syndrome

Sternbach's Criteria for Serotonin Syndrome (1991)

1. Recent addition or increase in a known serotonergic agent
2. Absence of other possible aetiologies (infection, substance al
3. No recent addition or increase of a neuroleptic agent
4. At least three of the following symptoms:
    - Mental status changes (confusion, hypomania)
    - Agitation
    - Myoclonus
    - Hyperreflexia
    - Diaphoresis
    - Shivering
    - Tremor
    - Diarrhoea
    - Incoordination
    - Fever

Serotonin Syndrome Hunter Criteria

- Dunkley et al (2003) improved on the sensitivity and specificity of the Sternbach criteria
- Hunter Area Toxicology Service (HATS) located in Australia
- HATS database yielded 2,222 cases of overdose with at least one SSRI
- CART – Classification and Regression Trees – software uses statistics rather than experience to describe a dataset

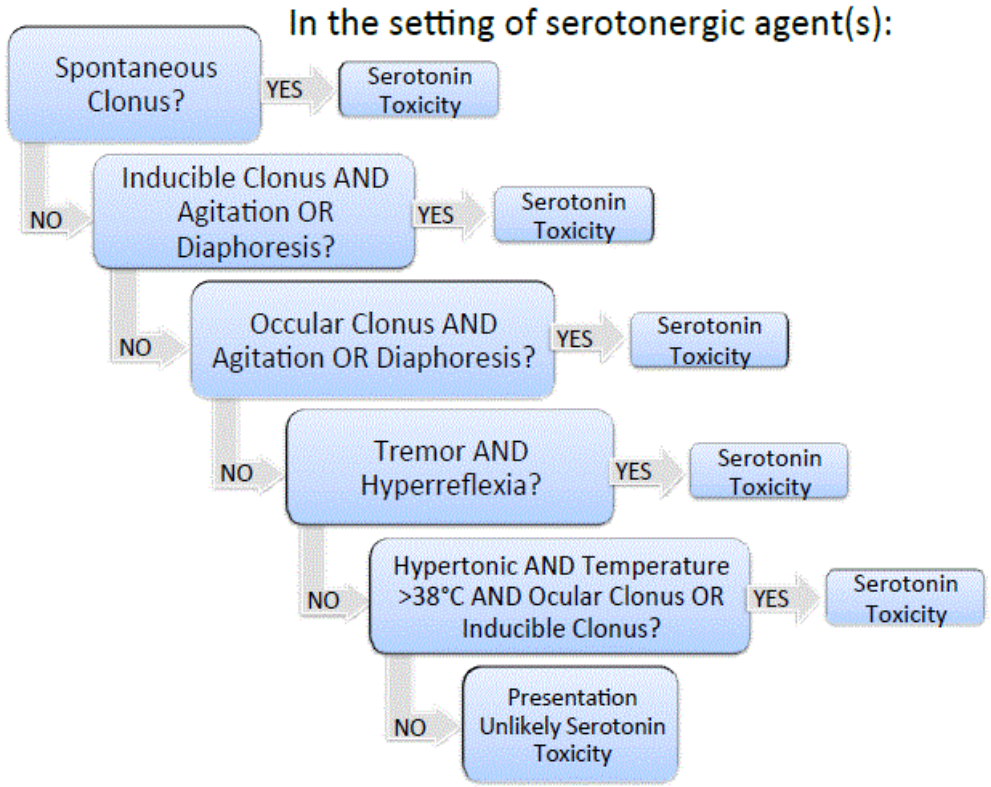
Hunter Serotonin Toxicity Criteria

Decision Rules (2003)

Hunter Serotonin Toxicity Criteria: Decision Rules
In the presence of a serotonergic agent: 1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES 2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES 3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES 4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES 5. ELSE IF (hypertonic = yes) AND (temperature > 38°C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES 6. ELSE serotonin toxicity = NO

Hunter Serotonin Toxicity Criteria:

Decision Rules



Hunter Criteria for Serotonin Syndrome

- Simpler, more sensitive (84% vs 75%), and more specific (97% vs 96%) than Sternbach criteria

DSM-5
Diagnosis of SS

- Not dealt with!
- This in spite of the known morbidity and mortality, and the frequency of DDIs

Serotonin Syndrome

- New important serious cases of toxicity recently described, e.g., fatal interaction between methylene blue and venlafaxine
- Top WMC et al, 2014 The Netherlands Journal of Medicine, pp 179-81

Serotonin Syndrome Recent Fatal Case

- 70 Y.O.F with primary hyperparathyroidism
- Rx venlafaxine 75 mg bid, last dose taken morning of surgery
- 1 hour before anesthesia, 1 g methylene blue given IV, to visualize pathological tissues in the PT glands

Serotonin Syndrome Recent Fatal Case

- 1 hour after procedure, became agitated and then MSE deteriorated
- Reduced LOC, pupillary dilatation, ocular clonus, dysarthria, hyperreflexia
- Further deterioration with profuse sweating, hypersalivation
- Opisthotonus 9 h after MB/36.4 deg C
- Gradual increase in temperature to peak of 43 deg C at 21 hours after MB
- Death from circulatory collapse

Prevention of Serotonin Syndrome

- Prevention
  - Avoid MAOI and serotonergic drugs
  - Take care with combinations of serotonergic drugs
  - History of sensitivity to serotonergic agents
- Early recognition

Treatment of Serotonin Syndrome

- Cessation of offending agents
- General supportive measures, cooling, hydration, etc.
- Ventilatory support if needed
- Serotonin antagonists – cyproheptadine (Periactin), ketanserin
- BZDZ
- Death rate low with treatment

Overlap between NMS and SS

- Hyperthermia (only if SS severe)
- Diaphoresis
- Rigidity (only if SS severe)
- Changes in mental status
- Autonomic activation and instability
- But quite different in cause, other signs and symptoms, treatment, and time course

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Questions and discussion