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LTC Nurse-Led Outreach

Interdisciplinary collaboration for a resident with complex agitation: Could this be serotonin syndrome?

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Disclosures

No conflicts of interest to declare

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Workshop Objectives

1. Explore collaborative models that coordinate cross-sectoral programs, services and care delivery to support complex residents, including those with, or at risk for, responsive behaviours associated with dementia, complex mental health, substance use and/or other neurological conditions in the LTC setting.
2. Obtain practical insight into recognizing, assessing and managing residents where a diagnosis or potential diagnosis of serotonin syndrome may be considered.
3. Present and discuss a clinical case of complex agitation with suspected serotonin syndrome.

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Collaborative Models & Programs

"Interprofessional care has the potential to increase the capacity of the Ontario health care system, improve patient care, and increase patient satisfaction"

(Hanna, 2016 in OMA Policy: Interprofessional Practice)

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Interprofessional Collaboration

Cross sectoral support within the LTC home includes the following:

- MD/NP
- Pharmacist
- BSO Team
- Recreation Therapist
- Geriatric Psychiatry
- GeriMedRisk
- Psychogeriatric Resource Consultant

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Serotonin Syndrome

Serotonin Syndrome (SS)

- A drug induced condition
- Excessive serotonergic activity in the central and peripheral nervous systems
- Encompasses a spectrum of clinical features ranging from minor symptoms to death
- Serotonin toxicity is often used to describe milder symptoms of serotonin syndrome

Causes of Serotonin Syndrome

- Medications resulting in an increase in serotonin levels
    - Inhibit serotonin breakdown
    - Inhibit serotonin reuptake
    - Serotonin agonist
    - Increase serotonin release from presynaptic terminals

- Drug interactions resulting in increases in any serotonergic medication
- Intentional or unintentional overdoses
- Will occur in 14-16% of patients overdosing on SSRI
- Overlapping transitions between serotonergic medications

Liu, Yang, Fei, Xu, Tong, Liu, Ni, Zang, & Wang, 2019; Thanacoody, 2015; Wang, Vashistha, Kaur & Houchens, 2016; Werneke, Jamshidi, Taylor & Ott, 2016

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Serotonin Syndrome

Serotonin Syndrome Incidence

- With increased use of serotonergic agents to treat depression, incidence of serotonin syndrome as also increased
- Incidence is difficult to assess due to probable underreporting, lack of recognition of the syndrome and misdiagnosis
- One study found a reported incidence of 0.5-1 case per 1000 patient months of treatment
- However the same survey identified that 85% of respondents were not familiar with serotonin syndrome

Wang et al., 2016

Serotonin Syndrome

- Symptom onset occurs after medication initiation which alters serotonin levels
- Onset of symptoms occurs within minutes to hours after starting a second serotonergic drug or following overdose; ~60% patients present with symptoms within 6 hours
- Acute toxicity occurs within 24hrs of medication initiation in ~70% of cases
- Subacute toxicity occurs within 24hrs of medication initiation in ~60% of cases
- Case reports of late onset symptoms across all age groups including geriatric cases
- Likely underreported, unrecognized or confused with other syndromes
- In severe cases, seizures, hyperthermia, rhabdomyolysis, renal failure and DIC may occur

Liu et al., 2019; Thanacoody, 2015; Wang, Vashistha, Kaur & Houchens, 2016; Werneke, Jamshidi, Taylor & Ott, 2016

Serotonin Syndrome Symptoms

- Symptoms are variable and non-specific
- Symptoms include neuromuscular, autonomic and mental status changes but all 3 features are not always present

Changes in mental state

- restlessness/agitation, confusion
- ~40% have mental status changes

Neuromuscular symptoms

- tremor, myoclonus, hyperreflexia
- ~50% have neuromuscular hyperactivity

Autonomic symptoms

- Abdominal cramping, hyperpyrexia (fever), diaphoresis, hypertension and potentially death
- ~40% have autonomic instability

Liu et al., 2019; Thanacoody, 2015; Wang, Vashistha, Kaur & Houchens, 2016; Werneke, Jamshidi, Taylor & Ott, 2016

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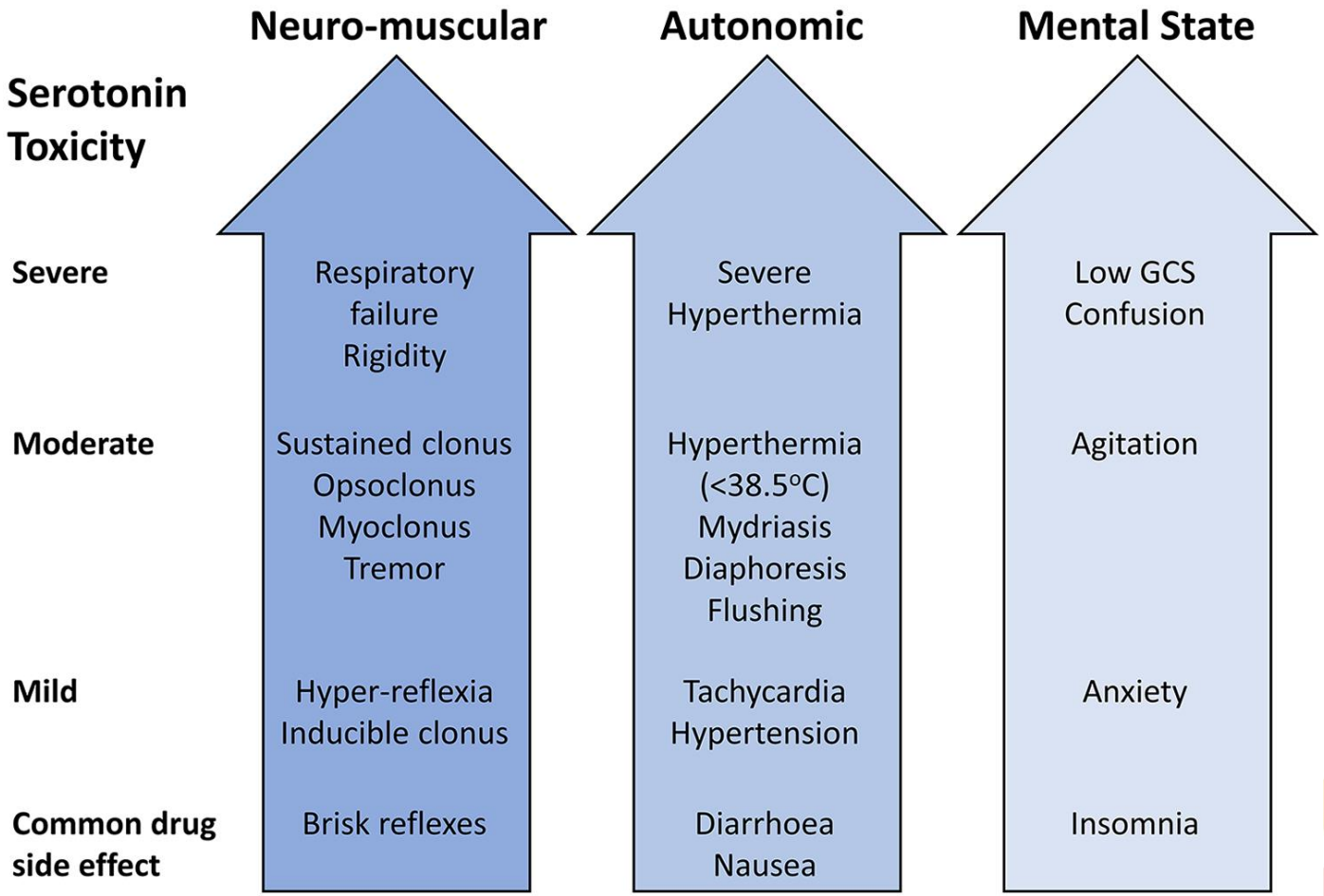
Clinical Features of Serotonin Syndrome



Scotton, Hill, Williams & Barnes, 2019

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Serotonin Syndrome: Diagnosis

Diagnosis is based on clinical findings

- Serotonin levels are poorly correlated to clinical symptoms
- Diagnosis requires a low threshold for suspicion, excellent history and physical exam
- Not all cases are identified as “rapid onset” and only a few cases are noted to present with hyperthermia
- In mildest form, symptoms often misattributed to other causes and in severe form can be mistaken for neuroleptic malignant syndrome
- Three diagnostic criteria systems (Sternbach, Radmski & Hunter classifications)
- Laboratory abnormalities may include metabolic acidosis, elevated serum creatinine kinase and transaminases and renal impairment

Liu et al., 2019; Thanacoddy, 2015; Wang et al., 2016; ThanWerneke et al, 2016

Diagnosis Criteria for Serotonin Syndrome

Criteria	Cause	Symptom	Diagnosis
Sternbach (1991)	Serotonergic agent	Agitation, fever, hyperreflexia, incoordination, diaphoresis, diarrhea, mental state change, myoclonus, shivering diarrhea, tremor	• At least 3 symptoms • r/o other causes • Adapt from other neuroleptic use or increase dosage
Radomski (2000)	Serotonergic agent	Major sx: diaphoresis, shivering, tremor, semi coma/coma, rigidity, myoclonus, impaired consciousness, fever, elevated mood Minor sx: akathisia, dilated pupils, hypertension, hypotension, incoordinaton, insomnia, restlessness, tachycardia, diarrhea, tachypnea or dyspnea	• 4 major symptoms • r/o other possible causes like psychiatric disorders, infection or change in neuroleptic meds
Hunter (2003)	Serotonergic agent	• Spontaneous clonus • Tremor plus hyperreflexia • Ocular clonus with agitation or diaphoresis • Inducible clonus plus agitation or diaphroresis • Hypertonia with temp >38C plus ocular clonus or inducible clonus	• Meets at least one symptom

Liu, Y., Yang, H., Fei, H., Xu, P., Tong, H., Liu, Y., Ni, J., Zang, Q., Wang, J. (2019)

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Serotonin Syndrome vs. Other Toxidromes

TOXIDROME	CAUSATIVE AGENT	ONSET, RESOLUTION	VITAL SIGNS	PUPILS	MENTAL STATE	OTHER CLINICAL FEATURES
Serotonin syndrome	Serotonergic drugs	Sudden <24 h Most resolve with 24 h with treatment (though 25% develop symptoms after >24 h)	Hyperthermia (>41.1°C), tachycardia, hypertension, and tachypnoea	Mydriasis	Delirum, agitation, and coma	Neuromuscular hyperactivity (tremor, myoclonus, hyperreflexia, and clonus), diaphoresis, and hyperactive bowel sounds
Neuroleptic malignant syndrome	Dopamine antagonists and dopamine withdrawal	Slower onset (days to weeks) Up to 10days to resolve with treatment	Hyperthermia (>41.1°C), tachycardia, hypertension, and tachypnoea	Normal or mydriasis	Delirium, agitation	Neuromuscular hypoactivity ('lead-pipe' rigidity and bradykinesia) Hypoactive bowel sounds
Anticholinergic toxicity	Anticholinergic agents	Sudden <24 h Resolves hours to days with treatment	Hyperthermia (usually <38.8°C), tachycardia, hypertension (mild), and tachypnoea	Mydriasis	Hyper-vigilance, agitation, hallucination, delirium with mumbling speech, and coma	Normal muscle tone and reflexes Dry flushed skin and mucous membranes Hypoactive bowel sounds Urinary retention Hyperkinesis (myoclonus, choreoathetosis, and picking behaviour) Seizures (rare)
Malignant hyperthermia	Inhalational anaesthetics and depolarising muscle relaxants (succinylcholine)	Very sudden (mins to hours) Resolves 24-48 h with treatment	Hyperthermia (can be as high as 46°C), tachycardia, hypertension, and tachypnoea	Normal	Agitation	Rigour-mortis like rigidity Hyporeflexia Hypoactive bowel sounds Rising end-tidal CO_2 Mottled skin with flushing and cyanosis

Scotton, Hill, Williams, & Barnes. (2016). *International Journal of Tryptophan Research, 12 (1-14)*
Foong, Grindrod, Patel & Kellar, 2018; Foong, Patel, Kellar, & Grindrod, 2018.

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Causes of Serotonin Syndrome

Many mechanisms for increasing serotonin effects – many medications may contribute to this syndrome

Medications resulting in an increase in serotonin effects

- Increase the production of serotonin
- Increase serotonin release from presynaptic terminals
- Serotonin agonist – stimulating the serotonin receptor on the post-synaptic terminal
- **Inhibit serotonin reuptake from the synaptic cleft**
- **Inhibit serotonin metabolism/breakdown**

Other Mechanisms for increasing serotonin levels

- Drug interactions resulting in increases in any serotonergic medication
- Intentional or unintentional overdoses
- Overlapping transitions between serotonergic medications

Medications Contributing to Serotonin Syndrome

Medications Inhibiting Serotonin Reuptake

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, vortioxetine**

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- **Venlafaxine. desvenlafaxine and duloxetine**

Tricyclic Antidepressants (TCAs)

- **Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline**

Foong, 2018; Thanacoody, 2017; Wang, 2016

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Medications Contributing to Serotonin Syndrome

Other Medications Inhibiting Serotonin Reuptake

- Trazodone
- St. John's Wort
- Synthetic opioids
  - meperidine, pentazocine, tramadol, fentanyl
- Dextromethrophan
- Antihistamines
  - Chlorpheneramine, brompheneramine

- Opioids similar in structure to morphine do NOT inhibit serotonin reuptake and contribute to serotonin toxicity
  - Morphine, hydromorphone, codeine, oxycodone, buprenorphine

Foong, 2018; Thanacoody, 2017; Wang, 2016

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Medications Contributing to Serotonin Syndrome

Medications inhibiting metabolism of serotonin

- Monoamine oxidase (MAO) – responsible for metabolism of serotonin
- Monoamine Oxidase Inhibitor (MAOIs) inhibit the enzyme resulting in increased presynaptic serotonin levels
  - **Phenelzine, tranylcypromine: Non-selective, irreversible MAOIs**
  - **Linezolid: Non-selective, reversible MAOI**
  - **Moclobemide: Selective, reversible MAO A inhibitor**
  - **Selegeline, rasagiline: Selective, irreversible MAO B inhibitors**
- Combination of an MOA inhibitor with a serotonin reuptake inhibitor is a high risk combination for SS

Foong, 2018; Thanacoody, 2017; Wang, 2016

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Medications Contributing to Serotonin Syndrome

Other medications potentiating serotonin activity include:

- **Medication increasing serotonin synthesis**
  - tryptophan
- **Medication increasing serotonin release**
  - mirtazapine
  - Amphetamines
  - Illicit drugs: MDMA (Ecstasy), cocaine
- **Serotonin agonists**
  - Buspirone, triptans (e.g. sumatriptan), lithium

Foong, 2018; Thanacoody, 2017; Wang, 2016

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Medications Contributing to Serotonin Syndrome

Experts disagree on the list of medications contributing to serotonin syndrome

Strong Evidence for Contributing to Serotonin Syndrome	Weaker Evidence for Contributing to Serotonin Syndrome
• MAOIs, including linezolid • SSRIs, SNRIs, TCAs, St. John's Wort • Synthetic opioids and dextromethorphan • Chlorpheneramine • Tryptophan • Illicit drugs: MDMA, amphetamines, cocaine	• triptans • mirtazapine • buspirone • Lithium • trazodone

Foong, 2018

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Medications Contributing to Serotonin Syndrome

- SSRIs, SNRIs, TCAs are largely cleared from the body via hepatic metabolism
- Many medications can inhibit the cytochrome P450 enzymes responsible for the metabolism of these medications
  - CYP P450 1A2, 2C19, 2D6 or 3A4 isoenzymes
  - Resulting in elevated levels of serotonergic medications
- Some medications causing increase levels of SSRIs, SNRIs or TCAs include
  - Fluoroquinolones, esomeprazole, quinidine, bupropion, erythromycins, grapefruit juice and many, many others
- These interactions are many and complex
  - Engage your pharmacist to evaluate possible drug interactions

Adapted from Drug Interactions Flockhart Table. Accessible at https://drug-interactions.medicine.iu.edu/MainTable.aspx

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Serotonin Syndrome: Other Risk Factors

Genetic Polymorphisms

Some individuals are more sensitive to serotonergic effects and serotonin syndrome due to genetic polymorphisms

- affecting the serotonin transporter protein
- affecting the serotonin receptor
- affecting cytochrome P450 metabolic enzymes

Risk of serotonin syndrome is not predictable due to these individual genetic variations

Francescangeli , 2019

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Serotonin Syndrome Prevention

CAUTION must be used when

- Increasing the dose of an SSRI, SNRI or TCA
- combining or switching between antidepressants or other agents with serotonergic activity
- if adding a drug that inhibits the CYP P450 1A2, 2C19, 2D6 or 3A4 isoenzymes

Monitor

- If milder symptoms of restlessness, agitation, tremor develop then BP and temperature should be monitored
- Offending agents should be discontinued if BP or temperature begin to rise and supportive therapy initiated

Serotonin Syndrome Prevention

- **To avoid precipitation of serotonin syndrome when switching between antidepressants**

  - Allow serotonergic medications to wash out prior to initiating another serotonergic agent

  OR

  - Cross taper to minimize risk of excessive serotonergic effects

Foong et al, 2018; Scotton et al, 2019; Werneke et al., 2016

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Antidepressant Elimination Half-Life

Agent	$T_{1/2}$ (hrs)	$T_{1/2}$ (hrs) metabolites	Washout period
Amitriptyline	16	30	5 dys
Clomipramine	32	70	12 dys
Nortriptyline/ desipramine	30		5 dys
Citalopram	36		6 dys
Fluoxetine	50	**240**	5-6 wks
Venlafaxine	5	11	1-2 dys
Duloxetine	11		1-2 dys
Trazodone	6		1dy

Adapted from Goodman & Gilman's The Pharmacological Basis of Therapeutics

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Antidepressant Cross Tapering

No clinical practice guidelines on cross tapering

- Taper agents to avoid withdrawal
  - Withdrawal symptoms seen primarily with serotonergic agents, i.e. TCA,s, SSRI's and SNRI's with short $t_{1/2}$
  - Fluoxetine will self-taper due to its' long $t_{1/2}$
  - taper over period of 1-4 weeks; longer tapers usually employed with higher doses

- Initiate the 2nd agent and taper up to allow tolerance to develop
  - Aim to reach steady state of the new agent as the initial drug is effectively cleared from the body
  - For fluoxetine, the 2nd agent should not be initiated until week 4 or 5 post-discontinuation

- Monitor for symptoms of serotonin toxicity throughout the cross taper
  - Reduce dose of delay titration of 2nd agent if needed

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Serotonin Syndrome Management

1. Discontinue serotonergic medications
2. Provide supportive care
   - VS monitoring (temp, BP, P)
   - Monitor renal function
   - Fluids to replace insensible fluid loss or correct hypotension
   - Avoid physical restraint
   - 70% will improve within 24hours
3. Benzodiazepines
   - Anxiolytic and muscle relaxant properties help to manage symptoms
4. Standard cooling measures for hyperthermia
   - Antipyretics are not effective
5. For severe symptoms
   - Maintain airway
6. Serotonin antagonist use – off-label
   - cyproheptadine
   - Some anecdotal reports of success but no evidence of significantly different outcomes as compared with supportive care alone
7. Beta blocker – propranolol
   - For management of tachycardia

Foong, Patel, Kellar & Grindrod, 2018; Thanacoody, 2015.

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Serotonin Syndrome Prognosis

- Serotonin Syndrome spectrum of dose dependent clinical features
- Clinical features range from mild to live threatening (severe toxicity)
- Prognosis is favourable if syndrome is recognized early, causative agent stopped and complications treated
- Requires clinician to have high clinical suspicion for serotonin syndrome
- Most cases of Serotonin Syndrome, symptoms resolve within 24 hours of stopping the drug and where the drug has active metabolites or a longer half life, symptoms can last longer
- In milder cases, clinician and patient collaboratively need to weigh the benefits and risks before restarting serotonergic agent (suggested at a lower dose)

Scotton et al., 2019

Clinical Case: Complex Agitation

75 year old resident

PMH:
Mixed dementia with BPSD
Anxiety disorder; ?PTSD
OA
GERD
Vit B12 deficiency

PSH:
None

Allergy: Citalopram (unknown reaction)
?polymorphism causing increased sensitivity to serotonergic medications

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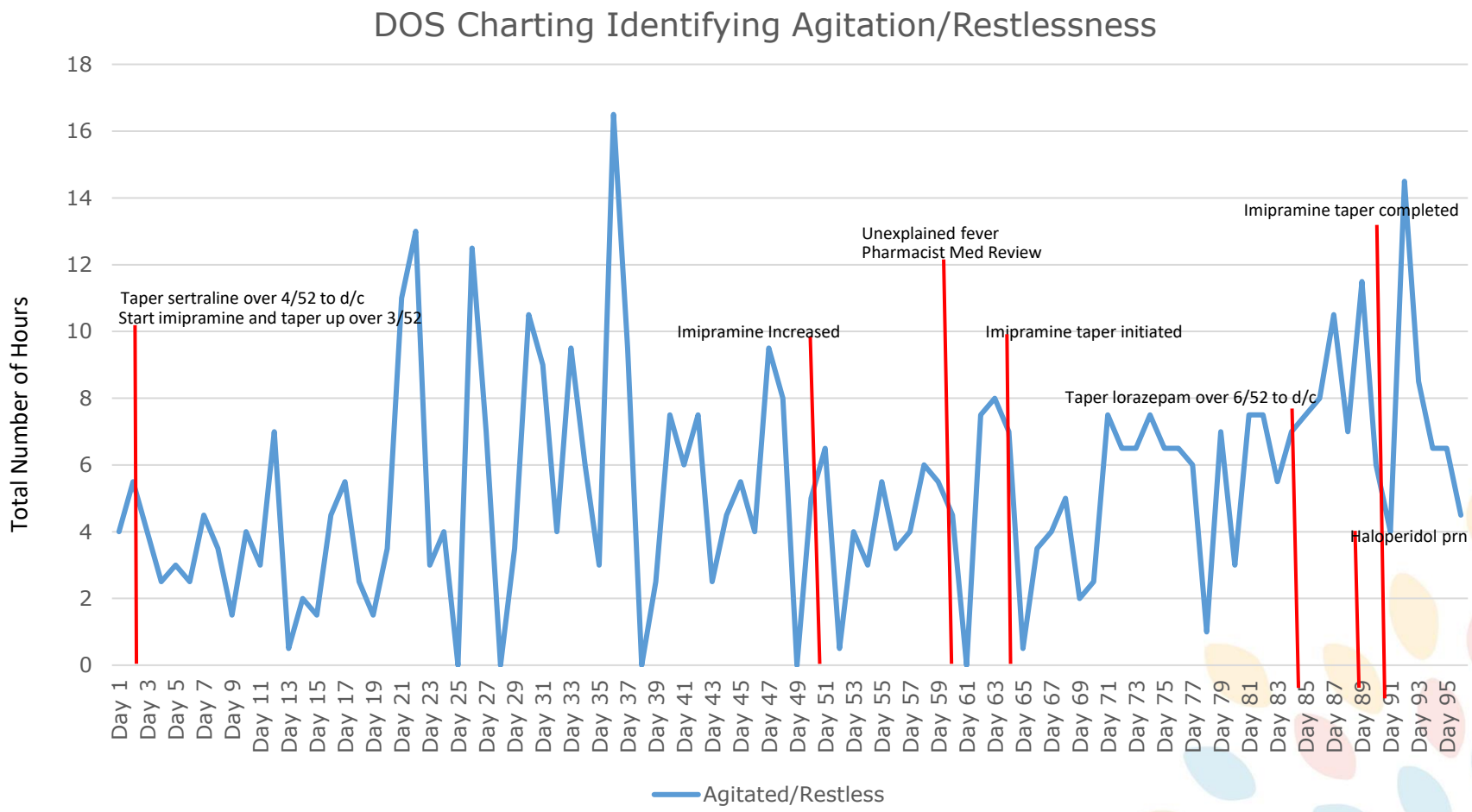
Clinical Case: Complex Agitation

- In LTCH for a few years
- Involvement with MD, geriatric psychiatry, pharmacist, BSO team and NP (prn basis)
- Ongoing review including review of DOS charting with team
- Initially ambulatory and has had progression with dementia and no longer ambulatory
- When ambulatory, noted to be pacing, but easily distracted and engaged in activities
- Multiple visits with psychiatry/geriatric psychiatry including lengthy hospitalization r/t anxiety/agitation
- Ongoing DOS charting identified anxiety, agitation, restlessness and some rigidity of extremities (however rigidity often associated with agitation and found to be purposeful), tremors, diaphoresis
- Multiple medication changes over time, recent increase in imipramine and found to have an unexplained fever

DOS Charting



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Medication History

2 year history of anxiety and agitation responding poorly to medication

- Escitalopram, trazodone, sertraline, venlafaxine, paroxetine, mirtazapine, lorazepam, propranolol, risperidone, nabilone, clonazepam, methotrimeprazine

Year 3

- First documented episode of diaphoresis
- Rocking movement – ?rhythmic muscular contractions/clonus
- Receiving
  - mirtazapine 30mg po at bedtime
  - Cross tapered from sertraline 200mg po daily to imipramine 25mg po BID and 100mg at bedtime has been initiated

1 month later

- Cross taper complete
- Unexplained fever, diaphoresis and muscle rigidity reported
- Agitation and anxiety continue
- Taking mirtazapine and imipramine
- Taper of imipramine initiated in response to symptoms

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Medication History

2 months later

- Remains agitated and anxious; no reports of other physical symptoms
- Imipramine taper completed, remains on mirtazapine 30mg/day
- Short course of levofloxacin before imipramine taper completed

3 - 6 months later

- MD notes agitation on one occasion

6 – 9 months later

- Verbally responsive behaviours noted on occasion
- Mirtazapine tapered and discontinued

10-12 months later

- Charting often indicates resident is calm and comfortable, no concerns noted
- Occasional reports of restlessness or verbally responsive behaviours
- Receiving melatonin for sleep, pregabalin, hydromorphone and nabilone for pain management, valproic acid for seizures

Complex Agitation: Could this be Serotonin Syndrome?

Pros	Cons
Medications • Imipramine and mirtazapine • Possible concerns with cross taper from sertraline to imipramine • Short course of levofloxacin may have increased imipramine levels • citalopram allergy – possible sensitivity to serotonin	**Medications** • Imipramine and mirtazapine – not considered a high risk combination • Timing of serotonerigic symptom onset and resolution do not clearly occur within 24hrs of medication changes
Symptoms • Agitation, ongoing despite treatment with SSRIs, SNRIs and TCAs • Pain, constipation managed to minimize responsive behaviours • Clonus?, muscle rigidity • Diaphoresis • Unexplained fever • Meets the Hunter criteria for SS • Resolution of symptoms following discontinuation of suspected medications	**Symptoms** • Agitation – symptom also associated with dementia or withdrawal from serotoninergic medications • Clonus? • Fever and diaphoresis – possible underlying infection? • Pneumonia was treated approx. 1 month after these symptoms

Consider serotonin toxicity with anxiety or agitation unresolved or aggravated by typical serotonergic therapies.

Target Serotonin Syndrome

def. Toxicity caused by excessive serotonin levels that results from a drug overdose or interaction

Assess the patient

Symptoms start within hours to 1 day of increasing a dose or adding a drug

Mild	Moderate	Severe
Nervousness	Hyperreflexia	Fever >38.5°C/101.3°F
Insomnia	Sweating	Confusion/delirium
Nausea/diarrhea	Agitation/restlessness	Sustained clonus/rigidity
Tremor	Inducible clonus	Rhabdomyolysis
Big pupils	Side-to-side eye movements	Death

Assess all drugs

Most cases involve 2 drugs that increase serotonin in different ways – full list on back

Prescription drugs

OTC and natural drugs

Illicit drugs

Rule out

Serotonin syndrome can look like other things; diagnosis requires an accurate drug history

Similar-looking conditions:
- Antidepressant Discontinuation
- Anticholinergic Toxicity
- Malignant Hyperthermia
- Neuroleptic Malignant Syndrome
- Meningitis/Encephalitis
- Drug Overdose
- Alcohol/Benzo Withdrawal

Remind all patients: **Non-toxic increases in serotonin can cause anxiety, restlessness and irritability for 1-2 weeks**

If you suspect serotonin syndrome

Don't wait, take action – it progresses rapidly

Stop the drug(s) → Refer patient to hospital → once symptoms are gone → Try other drugs or restart low doses slowly

Prevent serotonin syndrome

Stay alert – most cases can be prevented

- ✓ Use lowest effective dose
- ✓ Ask about illicit drug use
- ✓ Check drug monographs for tapering and wash-out periods
- ✓ Follow up 1-2 days after upping a dose or starting a new drug
- ✓ Reassess the need for a serotonin drug yearly
- ✓ Teach patients to recognize serotonin syndrome

AVOID: Group A with Group A or Group A with Group B

CAUTION: TWO or more Group B drugs especially when ONE is used at a high dose

MONITOR: If a patient uses a Group B drug and a second Group B drug is added, start low, increase the dose cautiously, and watch for symptoms for 24-48h after every change

Group A

Non-selective and irreversible MAOi A and B
Isocarboxazid
Isoniazid
Phenelzine
Tranylcypromine

Non-selective and reversible MAOi A and B
Linezolid

Selective and irreversible MAOi B
Selegiline (non-selective at higher doses)
Rasagiline

Selective and reversible MAOi A
Moclobemide
Methylene blue (non-selective at higher doses)

Group B

Antidepressants
Selective Serotonin Reuptake Inhibitors (SSRI): Paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, fluoxetine

Serotonin Norepinephrine Inhibitors (SNRI): Venlafaxine, desvenlafaxine, duloxetine

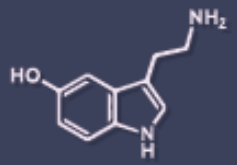
Tricyclic Antidepressants: Clomipramine, imipramine

Opioids and other pain medications
Tramadol, meperidine, methadone, fentanyl (unlikely with morphine, codeine, oxycodone, buprenorphine)

Cough, cold and allergy
Dextromethorphan ("DM"), chlorpheniramine

Natural health products
St. John's wort, L-tryptophan, diet pills

Illicit drugs
Ecstasy (MDMA), amphetamine, cocaine



Commonly listed but unlikely to cause serotonin syndrome
Triptans (e.g., sumatriptan)

Antidepressants: amitriptyline, mirtazapine, trazodone

Antiemetics: 5HT3 receptor antagonists (e.g., ondansetron), metoclopramide

Buspirone, lithium

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