What do I do with all these side effects?

Recognition and management of side effects from psychotropic medications

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Learning Objectives

- At the end of this session, participants will be able to:
  - Articulate common side effects to first line antidepressants
  - Describe initial steps in the management of sexual side effects and weight gain caused by SSRIs
  - Discuss the findings of serotonin syndrome that providers might see in clinic

Sadly, I am not cool enough to have disclosures

Case 1- Chad

- Chad is a 42 yo cis man whom you have been seeing in clinic for the past five years. He is generally healthy, though has been struggling with weight loss and management of his asthma. Over the past year, Chad has been struggling with symptoms of depression and generalized anxiety and agreed to a trial of sertraline (50 mg per day) at your last visit. He returns for follow-up (three months later) and tells you that his depression has improved some, but he does not like the medication as it's causing him to have sexual side effects. He reports erectile dysfunction and difficulty achieving orgasm.

Are his sexual side effects due to his SSRI?

Are his sexual side effects due to his SSRI?

- It is certainly likely (particularly given this presentation), but we don't really know

- Start consideration with an evaluation of the patient's history with sexual dysfunction
  - In what phase(s) of function is (are) problem(s) present?
    - Desire?
    - Arousal?
    - Orgasm?
  - How is the dysfunction characterized?
    - Physiological dysfunction?
    - Psychological dysfunction?
    - Combination?
  - When did the dysfunction start?
  - How closely associated with the possible offending agent is the dysfunction?

Sexual dysfunction due to SSRIs

- Reported rates of sexual dysfunction with SSRIs varies in the literature
  - More recent studies describe 25-80% incidence
  - Some of this is due to different agents having different effects and different study lengths, but also…
    - Patients are not good at spontaneously disclosing this information
    - Providers are not great at overtly asking about these side effects
- Roughly 25% of the general population describes some kind of sexual dysfunction

A. Serretti & A. Chiesa. Treatment-Emergent Sexual Dysfunction Related to Antidepressants. J Clin Psychpharmacol (2009)29; 259-266.

Sexual dysfunction due to SSRIs

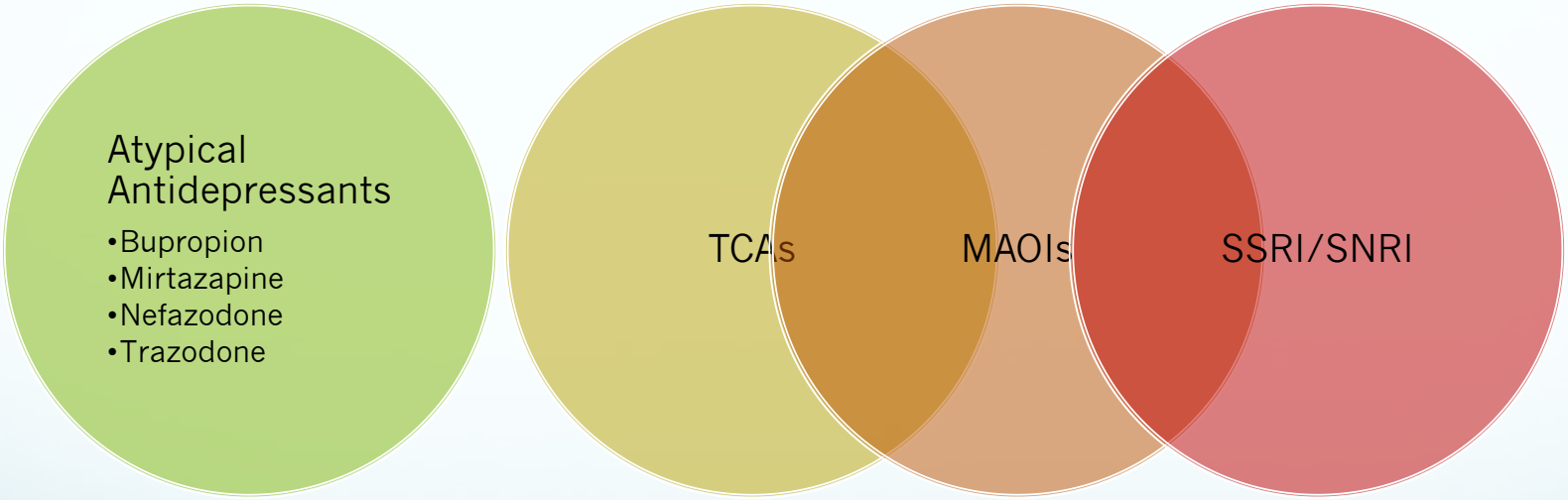
- Other complicating factors:
  - Most psychiatric pathology is bad for sexual functioning
    - **Anxiety**
    - Depression
    - Substance use
  - Patients have comorbid medical conditions
    - Vascular function
    - Neural function
    - Endocrine function

Sexual dysfunction due to SSRIs

- SSRIs do cause physiologic sexual dysfunction
  - Can cause dysfunction at any phase of sexual activity, but the most common form of dysfunction is anorgasmia (partial or complete)
    - Thought to be mediated through increased activity at the 5HT-1B/1C/1D receptors

S. Seidman. Ejaculatory dysfunction and depression: pharmacological and psychobiological interactions. International Journal of Impotence Research (2006)18; S33-S38..

Not all antidepressants are created equal



Higher doses tend to cause greater effects in terms of sexual dysfunction

A. Serretti & A Chiesa. Treatment-Emergent Sexual Dysfunction Related to Antidepressants. J Clin Psychpharmacol (2009)29; 259-266.

Chad Continued

- Chad describes quite an acute change in sexual functioning with initiation of sertraline (i.e. the next day). He has seen his interest in sex increase with treatment of depression and denies erectile dysfunction, but cannot achieve orgasm either alone or with his partner. He denies significant prior anxiety about sex though he has started to worry that his partner is frustrated with him.

  - Now what??

Management of SSRI associated sexual dysfunction

- Step 1: Clarify the presence of psychological vs physiological dysfunction
- Step 2: Consider giving it some time
  - Particularly effective early in treatment in younger patients with partial anorgasmia
- Step 3: Determine if the offending agent is worth keeping (i.e. you will try to treat the side effect) vs. it's time to move on (i.e. you are trying to avoid the side effect)

If the offending agent is not worth keeping

- Switch to something else:
  - Consider bupropion if:
    - Patient would benefit from activation
    - Anxiety is not a major part of the picture
    - Patient less likely to tolerate weight gain
  - Consider mirtazapine if:
    - Patient would like to sleep and needs to eat and/or has significant GI side effects to medications
    - Patient is anxious
  - Consider a different SSRI/SNRI or TCA if:
    - Patient has a lot of anxiety and/or cannot tolerate other options
  - Vilazodone (Viibryd) or vortioxetine (Trintellix) if the pt can afford it
  - Trazodone or nefazodone could be options, but can be hard to tolerate (trazodone) or not available (nefazodone)

E. Jing & K. Straw-Wilson. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review. Ment Health Clin [Internet] 2016;6(4): 191-196.

S.M. Stahl. Prescriber's Guide. Cambridge University Press. Cambridge. 2017.

If you want to keep the offending agent

- Can you successfully reduce the dose?
  - Often doses needed to reduce initial symptoms are higher than what is needed to maintain stability
- Consider augmentation with bupropion
  - Best study results from consistent administration at a dose of 300 mg/day or higher
  - Can also augment with mirtazapine or nefazodone though less data exists for this
- Consider PRN treatment with cyproheptadine
  - Case reports recommend 2mg-12mg one hour before sexual activity
    - I generally start with 4mg and then trial 8mg if partially effective
- Can consider PDE5 inhibitors

A. Javanbakht. As-Needed Use of Cyproheptadine for Treatment of Selective Serotonin Reuptake Inhibitor-Related Female Anorgasmia. J Clin Psychpharmacol 2015;35(1):91-93.

E. Jing & K. Straw-Wilson. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review. Ment Health Clin [Internet] 2016;6(4): 191-196.

Case 2 - Trinity

- Trinity is a 32 yo cis woman with a history of generalized anxiety disorder whom you have been seeing in clinic for the past 10 years. She had mostly treated her anxiety with intermittent therapy appointments in the past, but the pandemic has been really hard for her. She got laid off for a while, couldn't see her friends, lost her grandmother to COVID, and just could not stop worrying about what might happen next. You worked with her to add escitalopram in addition to her now regular therapy appointments. She returns after 6 months and tells you that her anxiety has been better, but she has been gaining weight (7 lbs since her last visit). She wants to know if there is anything to be done about this?

SSRI associated weight gain is real… but confusing

- Confusing because depression and anxiety can impact food intake and weight as well as lifestyle factors
  - Weight gain is not uncommon in depression, anxiety, or comorbid depression and anxiety
  - Can also see weight loss 2/2 depression in some cases
- Medical comorbidities are also very real

L.M. de Wit et al. Depressive and anxiety disorders: Associated with losing or gaining weight over 2 years? Psychiatry Research 227 (2015) 230–237.

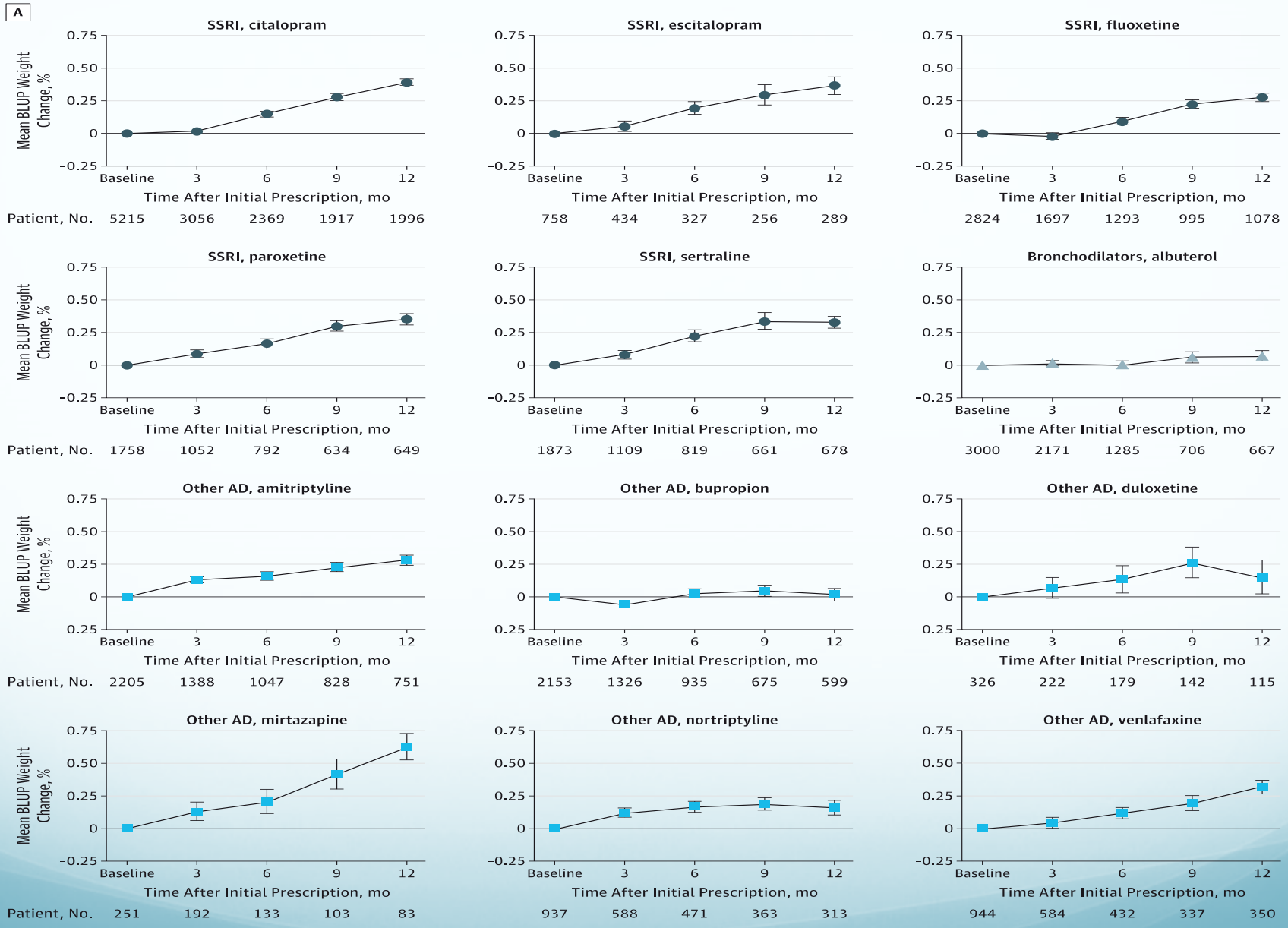
Which antidepressants and how significant is the effect?

- There is limited, good, long-term data showing the impact of antidepressants on weight gain
  - Most data comes from short-term and/or industry supported literature
    - Results are inconsistent and difficult to characterize

- Blumenthal et al – Naturalistic study of 22,610 patients receiving antidepressants followed over 12 month period utilizing an EHR

S.R. Blumenthal et al. An Electronic Health Records Study of Long-term Weight Gain Following Antidepressant Use. JAMA Psychiatry. 2014;71(8):889-896.

Figure 2. Mean Change in Weight After Index Prescription by Percentage of Baseline Body Mass Index Estimated by Best Linear Unbiased Prediction (BLUP)



S.R. Blumenthal et al. An Electronic Health Records Study of Long-term Weight Gain Following Antidepressant Use. JAMA Psychiatry. 2014;71(8):889-896.

Management of antidepressant associated weight gain

- Recommendations are limited but...
  - Step 1: Clarify the cause/causes of weight gain
    - What are the different factors at play?
      - What can be modified and what cannot?
  - Step 2: Consider where in the arc of weight gain the patient is at and where the patient is at in their treatment

Management of antidepressant associated weight gain

- Step 3: Do you want to keep the offending agent around or not?
  - Keep it:
    - Lifestyle modification?
      - Combine this with CBT work?
    - Dose reduction?
    - Some data for augmentation with topiramate
  - Get rid of it:
    - Consider switching:
      - Bupropion if pt can tolerate
      - Vilazodone or vortioxetine if sig anxiety and the pt can afford it
      - TCA/SNRI if significant anxiety symptoms are present and no insurance
      - Alternative SSRI
    - Nonmedication-based treatment

R.M.A. Hirschfeld. Long-Term Side Effects of SSRIs: Sexual Dysfunction and Weight Gain. J Clin Psychiatry. 2003;64[suppl 18]:20-24.

S.M. Stahl. Prescriber's Guide. Cambridge University Press. Cambridge. 2017.

Case 3 - Gina

- Gina is a 54 yo cis woman with a history of MDD and generalized anxiety disorder whom you have been seeing in clinic for the past year. She has migraines and chronic back pain. She came to you on fluoxetine at a dose of 60 mg per day and you started her on buspirone about nine months ago to better treat her anxiety. She is now taking 15 mg three times a day and she uses Imitrex as needed for her migraines. She was in a car accident two days ago and got a prescription for tramadol from an outside ED. She comes to clinic today reporting sweats, worsening anxiety, diarrhea, and nausea.

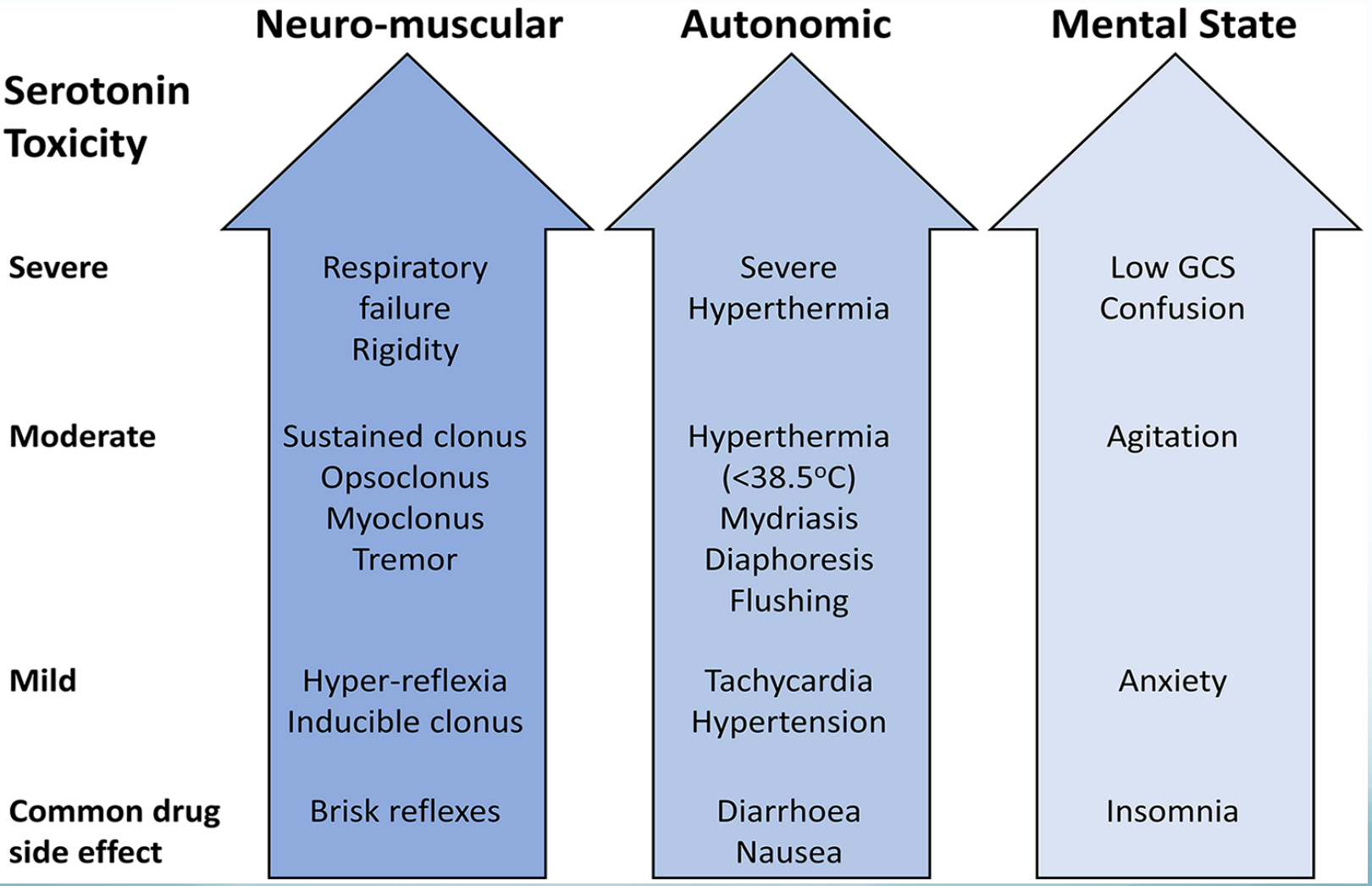
What is happening here?

Serotonin Syndrome

- Serotonin Syndrome (serotonin toxicity)
  - Condition caused by excessive serotonin in neuronal synapses leading to neuromuscular, autonomic, and mental status changes
    - There are no universally accepted diagnostic criteria
      - This has led to inaccurate case reports in the literature
  - True incidence and prevalence are unknown, particularly in subacute cases.
    - 15% of SSRI ODs lead to moderate sx of Serotonin Syndrome

A. Foong et al. Demystifying serotonin syndrome (or serotonin toxicity). Can Fam Physician 2018;64:720-727.

Clinical Features



W.J. Scotton et al. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. International Journal of Tryptophan Research 2019;12:1-14.

Diagnosis

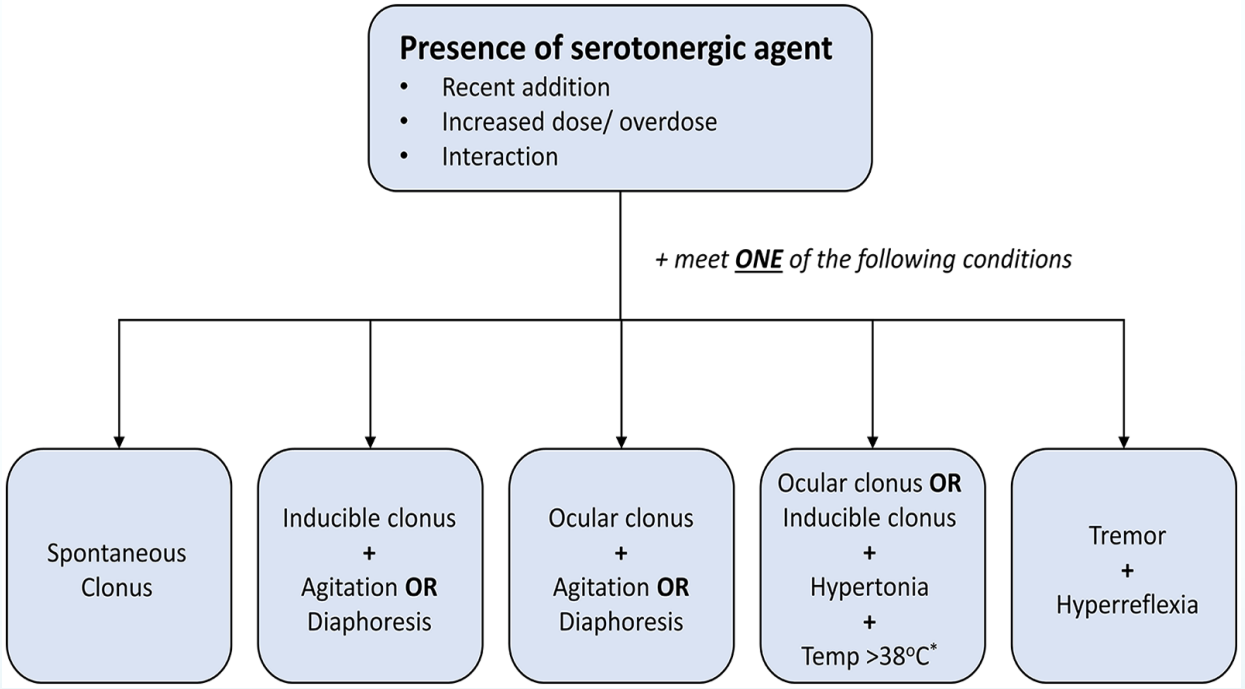
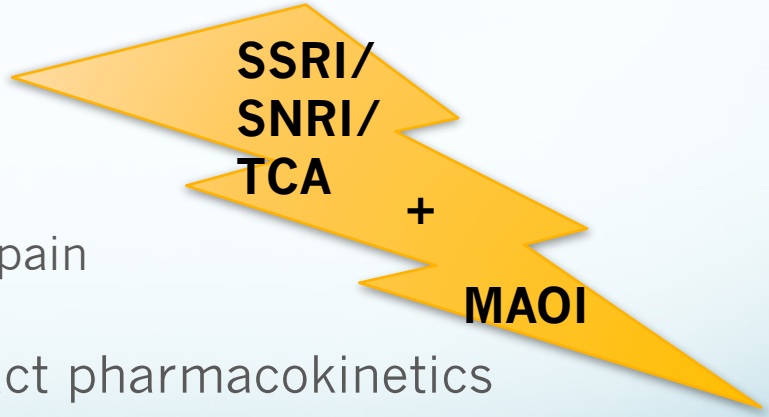


Figure 3. The Hunter Serotonin Toxicity Criteria: for diagnosing serotonin syndrome. Note that the requirement for the presence of some form of neuromuscular excitation, the sine qua non for a diagnosis of serotonin syndrome. *The presence of temperature ⩾38.5°C and/or marked hypertonia or rigidity (especially truncal) indicates severe SS with a risk of progression with respiratory compromise.

W.J. Scotton et al. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. International Journal of Tryptophan Research 2019;12:1-14.

Serotonin Syndrome

- Pathophysiology
  - Not entirely understood
    - There are 7 different serotonin receptor classes with 14 different subtypes
      - 5HT1 activity may lead to mild mental status changes
      - Significant 5HT2 activity may lead to more severe findings (with 5HT1 activity)
- What can cause it?
  - Lots of things
    - SSRIs, SNRIs, TCAs, MAOIs, SGAs
    - Agents to treat headaches, chronic pain
    - Substances of abuse
  - Now add in medications that impact pharmacokinetics
  - Genetic factors



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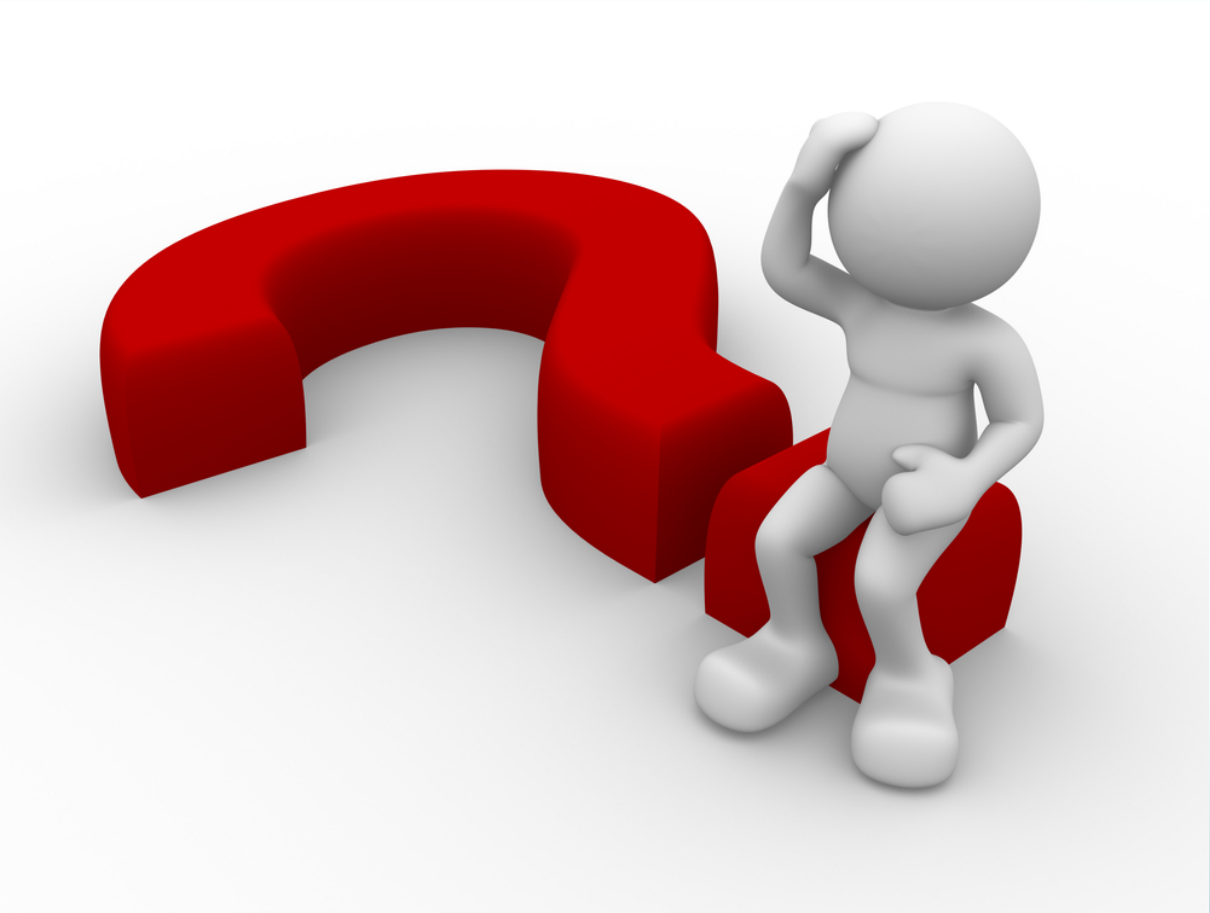
What should I do in the outpatient setting?

- If you are suspicious:
  - Get a good history
    - Onset and timing
    - Other agents
    - OD potential
  - Do a good exam
    - Including a neurological exam
- Mild toxicity, when everything is known and moving in the right direction, the drug half-lives are short, and the patient is highly capable and has good support, might be able to be managed with removal of the offending agent and close monitoring
- Moderate to severe toxicity and/or when details are unknown will require more urgent workup and closer, supportive care

A. Foong et al. Demystifying serotonin syndrome (or serotonin toxicity). Can Fam Physician 2018;64:720-727.
W.J. Scotton et al. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. International Journal of Tryptophan Research 2019;12:1-14.

How should I approach this practically?

- Serotonin toxicity is quite rare, even on two serotonergic agents
  - Realistically, many patients tolerate multiple possible offenders
- Onset is most likely in the setting of acute overdose or significant changes
  - Generally within 24-48 hours
    - Can depend on the agent
    - Unclear how specific this is in the case of mild symptoms
- Your antenna should go up when you notice multiple symptoms, across domains, immediately following a change
  - Neuromuscular, autonomic, mental status

W.J. Scotton et al. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. International Journal of Tryptophan Research 2019;12:1-14.

Questions?