Serotonin Syndrome

Serotonin syndrome is an iatrogenic disorder induced by pharmacologic treatment with Serotonergic agents that increases serotonin activity; in addition, there is a wide variety of clinical disorders associated with serotonin excess; the frequent concurrent use of serotonergic and neuroleptic drugs and similarities between serotonin syndrome and neuroleptic malignant syndrome can present the clinician with a diagnostic challenge

ANESTHETIC CONSIDERATIONS:

- Emergency, potentially fatal complication of serotonergic drugs, requiring simultaneous assessment & treatment
- Potentially life threatening interaction between medications
- Difficult diagnosis, requiring high index of suspicion (difficult to distinguish from MH and NMS)
- Consideration for underlying psychiatric disorder
- Treatment of complications including:
    - Hyperpyrexia, DIC, seizures, coma, muscle rigidity, autonomic instability, N/V, rarely rhabdomyolysis

ANESTHETIC GOALS:

- Stop offending medications and provide supportive care
- Avoid drugs which may exacerbate
- Rule out high risk conditions on differential diagnosis

HISTORY

- Detailed history will often reveal concomitant use of psychotropic medications
- Establish temporal relationship with initiation of new medication
- As NMS shares many clinical features with serotonergic syndrome, use of neuroleptics is of importance in ruling out / in NMS vs. serotonergic syndrome
- Features of serotonin syndrome
    - Confusion / agitation
    - Shivering, flushing, hyperpyrexia
    - DIC, seizures, coma, muscle rigidity
    - Myoclonus, hyperreflexia
    - Autonomic instability, nausea / vomiting
    - Rarely rhabdomyolysis

PHYSICAL

- **VITALS** - including temperature
- **CVS** - volume status, evidence of autonomic instability (postural changes in BP, resting tachycardia)
- **CNS** - mental status changes, muscle tone & reflexes
- **RESP** – signs of respiratory compromise / failure

INVESTIGATIONS

- **Labs**
    - CBC, lytes, BUN, Cr, CK (rhabdomyolysis)
    - Coagulation panel (DIC)
    - Pan-cultures – sepsis workup
    - Toxicology screen
- **Imaging**
    - ECG
    - Consider CXR & AXR to rule out secretory tumors

OPTIMIZATION

- Psychiatry / medicine / ICU consult
- Delay elective procedures
- Discontinuation of serotonergic agent
- Institution of supportive measures
    - ABCs
    - Antipyretics & cooling
    - Consider activated charcoal if recent ingestion (dialysis ineffective unless concurrent lithium overdose)
    - Use benzodiazepines to treat myoclonus, muscle rigidity & agitation (seizures)
        - Consider anticonvulsant (Dilantin)
        - NDNM blockers if benzodiazepines ineffective in eliminating rigidity
    - B-blockers may be useful due to their 5-HT blocking properties
        - Specifically, propranolol has demonstrated 5-HT_{1A} receptor antagonism in animal models
        - Additionally, nonspecific 5-HT_2 blockers, including methysergide and cyproheptadine, have been used with varying success, and there may be some role for phenothiazines
    - Hypertension – sedation +/- SNP
    - Hypotension – volume +/- NE
    - Airway protection and ventilatory support PRN

ANESTHETIC OPTIONS

- Local, regional, general

ANESTHETIC SETUP

- **Drugs**

- Avoidance of meperidine which can exacerbate syndrome
- Vasopressors, vasodilators (B-blockers - propranolol)

- **Equipment**
  - CAS monitors + CVP + art-line + temperature monitor / control

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Any if goals maintained
  - Avoid meperidine
- **Maintenance**
- **Emergence**

DISPOSITION & MONITORING

- Monitored setting postoperatively (ICU)

PATHOPHYSIOLOGY

- SSRIs are the most commonly prescribed class of antidepressants for the treatment of mild to moderate depression, panic and obsessive-compulsive disorders
  - Mechanism of action is through the inhibition of presynaptic reuptake of serotonin
  - Common side effects of SSRIs are insomnia, headaches, nausea & sexual dysfunction
- Serotonin syndrome is an iatrogenic condition, sharing some clinical features with NMS
  - Serotonin syndrome is the result of over-stimulation of 5-HT_{1A} receptors in central grey nuclei and the medulla and, perhaps, of over-stimulation of 5-HT_2 receptors
- Consider in overdose of SSRI or their use in combination with MAOi, TCAs, or meperidine
  - L-tryptophan, SNRIs, lithium, nefazadone & buspirone have also been implicated
  - Certain secretory tumors (oat cell lung carcinoma & carcinoid tumors) have been associated with the syndrome
  - Cases of mild serotonin syndrome have been reported in patients who have taken Hypericum perforatum (St. John's wort), an in-vitro 5-HT reuptake inhibitor, in conjunction with SSRIs

Table 1 Mechanisms of common drugs that influence serotonin syndrome

5-HT Synthesis	5-HT Release	Inhibit 5-HT Uptake	Inhibit 5-HT Metabolism	Postsynaptic Receptor Stimulation
L-tryptophan	Amphetamines	SSRIs	MAOIs	Buspirone
5-hydroxytryptophan	and derivatives	fluoxetine	phenelzine	5HT1 agonists
	dextramphetamine	paroxetine	tranylcypromine	sumatriptan
	metamphetamine	sertraline	isocarboxazide	zolmitriptan
	fenfluramine	fluvoxamine	selegiline	naratriptan
	dexfenfluramine	citalopram	meclobemide	rizatriptan
	phenteramine	Trazadone	St. John's wort	Lithium
	MDMA (ecstasy)	Nefazadone		Carbamazepine
	Cocaine	Venlafaxine		
	Reserpine	TCAs		
	Tetrabenazine	amitriptylline		
	Levodopa	imipramine		
	MAOIs	clomipramine		
	phenelzine	doxepin		
	tranylcypromine	desipramine		
	isocarboxazide	Bupropion		
	selegiline	Dextromethorphan		
	meclobemide	Tramadol		
		Meperidine		
		Sibutramine		
		Cocaine		
		St. John's wort		
		Amphetamine and derivatives		

- Four major symptoms:
  - Mental status changes
    - Confusion & restlessness
    - Convulsions, coma & death
  - Neuromuscular symptoms
    - Myoclonus & hyperreflexia
  - Autonomic dysfunction
    - Diaphoresis, tremor & hyperthermia
  - Gastrointestinal dysfunction
  - Also see:
    - Rhabdomyolysis, ARF, respiratory failure / ARDS (rare complications)
- Distinguishing SSRI syndrome from NMS:
  - Neuromuscular symptoms: in addition to tremor and rigidity that also occur in NMS, features such as shivering, ataxia, myoclonus, hyperreflexia, and ankle clonus may favor the diagnosis of serotonin syndrome
  - Gastrointestinal dysfunction: the presence of nausea, vomiting, and diarrhea is a unique feature not typically seen in NMS

Table 1: Situations that cause overstimulation of serotonin (5-HT_{1A}) receptors[2,3,8]

Situation	Associated drugs
Excess of precursors of serotonin or its agonists	Buspirone, L-dopa, lithium, LSD, L-tryptophan, trazodone
Increased release of serotonin	Amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, reserpine
Reduced reuptake of serotonin	SSRI, TCA, trazodone, venlafaxine, meperidine
Slowing down of serotonin metabolism	MAOI, e.g., isocarboxazid, selegiline

Note: LSD = lysergic acid diethylamide, MDMA = methylenedioxy-methamphetamine, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors.

- Mental status changes and autonomic dysfunction: these are similar to those seen in NMS, although some investigators believe that the degree of temperature elevation is not as high as in NMS

Box 1: Revised diagnostic criteria for serotonin syndrome[3,9]*

1. Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms plus 2 minor ones

Mental (cognitive and behavioural) symptoms

Major symptoms: confusion, elevated mood, coma or semicoma

Minor symptoms: agitation and nervousness, insomnia

Autonomic symptoms

Major symptoms: fever, hyperhidrosis

Minor symptoms: tachycardia, tachypnea and dyspnea, diarrhea, low or high blood pressure

Neurological symptoms

Major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia

Minor symptoms: impaired co-ordination, mydriasis, akathisia

2. These symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotonergic agent.

3. Infectious, metabolic, endocrine or toxic causes must be excluded.

4. A neuroleptic treatment must not have been introduced, nor its dose increased, before the symptoms appeared.

*Adapted from Radomski et al[9]

- Elevations in white blood cells, creatinine kinase levels, and liver enzymes are inconsistently and minimally elevated
- The course of this condition usually is benign, and most patients recover 1 to 7 days after withdrawal of the offending agent
- Appropriate supportive treatment may suffice
- Usually, patients recover without sequelae

REFERENCES

- Ener et al. – Serotonin syndrome and other Serotonergic disorders – Pain Medicine – 4(1)63-74(2003)
- Birmes et al. – Serotonin syndrome: a brief review – CMAJ - 2003; 168 (11)