Toxicology and Management of SSRI Overdose

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“All things are poison, and nothing is without poison. The dosage alone makes it so a thing is not a poison.”

–Paracelsus, founder of modern toxicology
Objectives

1) Review potential toxicities associated with an acute SSRI overdose

2) Identify pharmacological interventions used to treat patients who present with an acute SSRI overdose

3) Review a patient case pertaining to the management of an acute SSRI overdose
Background

• 11% of Americans use antidepressants
• Antidepressant use has steadily increased
• SSRIs most commonly prescribed antidepressant
• >52,000 SSRI overdoses annually
  • ~30,000 as polysubstance overdose
  • ~22,000 as single agent overdose
## SSRI Indications

<table>
<thead>
<tr>
<th>FDA-Approved</th>
<th>Off-Label</th>
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<tbody>
<tr>
<td>Major depressive disorder</td>
<td>Borderline personality disorder</td>
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<tr>
<td>Generalized anxiety disorder</td>
<td>Impulsive aggressive behavior</td>
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<tr>
<td>Bipolar I disorder</td>
<td>Body dysmorphic disorder</td>
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<td>Bulimia nervosa</td>
<td>Binge eating disorder</td>
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<td>Obsessive compulsive disorder</td>
<td>Raynaud phenomenon</td>
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<td>Social anxiety disorder</td>
<td>Neuropathic pain</td>
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<td>Panic disorder</td>
<td>Fibromyalgia</td>
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<tr>
<td>Post-traumatic stress disorder</td>
<td>Traumatic brain injury</td>
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<tr>
<td>Premenstrual dysphoric disorder</td>
<td>Selective mutism</td>
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<tr>
<td>Vasomotor menopause symptoms</td>
<td>Stuttering</td>
</tr>
</tbody>
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Patient Case

**CC**: Altered mental status

**HPI**: 25 y.o. woman presenting 12 hours after ingesting an unknown quantity of fluoxetine and citalopram

**PMH**: Major depressive disorder, PTSD, migraine, UTI

**Social**: 1 PPD smoker

**Family**: Non-contributory
Patient Case

Medication list:

• Ciprofloxacin 250 mg PO BID (UTI)
• Citalopram 20 mg PO daily (depression)*
• Quetiapine 300 mg PO daily (depression)
• Ondansetron 4 mg PO daily PRN (nausea)
• Sumatriptan 50 mg PO daily PRN (migraine)
Question 1

Which medication from LK’s list has an overlapping toxicity with a fluoxetine and citalopram overdose?

A. Ciprofloxacin  
B. Ondansetron  
C. Quetiapine  
D. Sumatriptan  
E. All of the above
**Presynaptic Nerve**

- Decreased reuptake:
  - SSRIs, SNRIs, TCAs, bupropion, opioids

- Decreased metabolism:
  - MAOIs, linezolid, methylene blue

**Postsynaptic Nerve**

- Increased release:
  - Cocaine, amphetamines, mirtazapine, buspirone

- Serotonin agonism:
  - Triptans, buspirone

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**Uptake Transporter**

Toxicology of SSRI Overdose

- **Serotonin syndrome**
  - Altered mental status
  - Autonomic hyperactivity
  - Clonus

- **Neurotoxicity**
  - CNS depression
  - Seizure

- **Cardiotoxicity**
  - QT-interval prolongation
  - QRS widening
Patient Case

After triage our patient is agitated, flushed, febrile, and is noted to have ocular myoclonus. The consultant and senior resident are in the resuscitation bay when an intern approaches you for help.

The intern wants to know about differential diagnoses, monitoring, and medications that have been utilized in treating SSRI overdose.
Serotonin Syndrome

- Serotonergic drugs
- Onset within 24 hours
- Agitation
- Hyperreflexia, clonus
- Hyperactive bowel sounds, N/V, diarrhea
- Hypertonia (especially in LE)

Neuroleptic Malignant Syndrome

- Dopamine antagonists
- Onset days to weeks
- Stupor, alert mutism
- Hyporeflexia
- Hypoactive/normal bowel sounds
- “Lead pipe” rigidity

Hyperthermia
Hypertension
Tachycardia
Tachypnea
“stiff”
Hunter Criteria for Serotonin Syndrome

• Serotonergic exposure and ≥1 of following:
  • Spontaneous clonus
  • Hypertonia
  • Tremor AND hyperreflexia
  • Inducible clonus AND agitation OR diaphoresis
  • Ocular clonus AND agitation OR diaphoresis
  • Febrile >38°C AND ocular clonus OR inducible clonus

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  - **Ocular clonus AND agitation** OR diaphoresis
  - **Febrile >38°C AND ocular clonus** OR inducible clonus

SSRI Overdose Monitoring

- **Vitals**
  - Core temp
  - HR
  - BP
  - RR
  - SPO2

- **Cardiac monitoring**
  - Baseline 12-lead ECG
  - Continuous monitor
  - QTc monitoring

- **Strict I/O**

- **Labs**
  - Co-ingested drugs
  - CK
  - CMP
  - CBC
  - PT/INR
  - aPTT
  - ABG
  - Urinalysis

- **Lumbar puncture**

- **Head CT**

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Sporer KA, Khayam-Bashi H. Acetaminophen and salicylate serum levels in patients with suicidal ingestion or altered Hurlbut, KM. Neuroleptic Malignant Syndrome and Serotonin Syndrome. The 5 Minute toxicology Consult. Philadelphia, PA: Lippincott Williams and Wilkins 2000; p 54
Serotonin Syndrome Management

- Removal of serotonergic agents
- Benzodiazepine administration
- Consider gastric decontamination
- Consider paralysis and intubation
- Consider cyproheptadine
Cyproheptadine in Serotonin Syndrome

- 5-HT2 antagonism at high doses
- PO/NGT route only
- 12 mg followed by 2 mg Q2H initially
- 4-8 mg Q6H for maintenance
- Only consider in moderate-severe cases
- ADE: Sedation, confusion, hypotension, palpitations, tachycardia

Presynaptic Nerve

Postsynaptic Nerve

Serotonin

Serotonin Receptors

Uptake Transporter

SSRI

Cyproheptadine

Serotonin Syndrome Management

• Kapur, et al in vivo study
• Basis of cyproheptadine use in serotonin syndrome
• Included 2 healthy adult volunteers
• Cyproheptadine 4 mg vs 6 mg TID for 6 days
• Evaluated 5-HT2 receptor occupation

• Results:
  • 85% receptor blocking in 4 mg TID subject
  • >95% receptor blocking in 6 mg TID subject
Patient Case

Using Hunter’s Criteria the intern diagnoses our patient with serotonin syndrome and enters orders to obtain a 12-lead ECG, draw labs, initiate parenteral fluids, and place the patient on 1-to-1 observation for suicidality.

Minutes later the patient has a tonic-clonic seizure.
Question 2

What would you choose as your initial treatment option for this patient’s seizures?

A. Fosphenytoin
B. Levetiracetam
C. Lorazepam
D. Phenobarbital
E. Valproic acid
Neurotoxicity in SSRI Overdose

• CNS depression
  • Extension of pharmacological activity

• Seizures
  • Early finding in overdose
  • Most common in citalopram, escitalopram
  • Dose-related risk increase
  • Typically noted in concentrations 40x therapeutic levels
Neurotoxicity in SSRI Overdose

• Initial seizure management
  • Lorazepam 2-8 mg IV q 10-15 min PRN
  • Diazepam 5-10 mg IV q 5-10 min PRN

• Refractory seizure management
  • Phenobarbital 10-20 mg/kg IV
  • Propofol 0.5-2 mg/kg IV bolus followed by 20 mcg/kg/min IV infusion and titrated
  • Neuromuscular blockade and intubation
Pathway for Rhabdomyolysis

Myoclonus → Hyperthermia → Seizure → Rhabdomyolysis
Patient Case

After the seizure our patient is intubated and admitted to MICU. Later that day a repeat ECG is ordered and the following results are noted:

- Rate 96
- QRS 90
- QTc 541
Question 3

What medication will you administer if our patient develops torsades de pointes? (Rate 96, QRS 90, QTc 541)

A. Amiodarone
B. Calcium chloride
C. Magnesium sulfate
D. Metoprolol
E. Sodium bicarbonate
Cardiotoxicity in SSRI Overdose

- QT interval prolongation
  - QTc >500 msec associated with torsades de pointes
  - Elevated risk with baseline prolonged QT and co-ingestion
  - Delayed effect ~24 hours
  - Observed with citalopram and escitalopram ingestion


Cardiotoxicity in SSRI Overdose

- Treatment of torsades
  - Magnesium sulfate 1-2 grams IV over 15 min
  - Non-cardiac arrest: infuse in 100 mL D5W
  - Cardiac arrest: dilute in 10 mL and push IV
  - Baseline magnesium level not required
  - ADE: Hypotension, CNS depression, flushing

Mechanism of QRS Widening

- Na+
- SSRI
- Bicarbonate
Cardiotoxicity: QRS widening in SSRI Overdose

- Observed with massive ingestions
- Sodium bicarbonate 1-2 mEq/kg bolus
  - Bolus until narrowing observed
  - Follow with maintenance infusion 150 mEq/L
  - Sodium load and elevated pH displace drug from sodium channels
- ADE: Extravasation, alkalosis, hypernatremia, edema, heart failure exacerbation


Intravenous Lipids in SSRI Overdose

• First utilized in overdose in 1962
• Creates an intravascular “lipid sink”
• Historically used in anesthetic toxicity
• Use expanding to other lipophilic drugs
• ADEs: Thrombophlebitis, pulmonary infiltration, cholestasis, pancreatitis, infusion reaction

# Intravenous Lipids in SSRI Overdose

## Eren-Cevik, et al
- Case series of 10 adult overdoses receiving intravenous lipids
- 7 antidepressants, 2 SSRIs
- Both SSRI overdoses polypharmacy
- 9 of 10 patients survived overdose
- Improvements in GCS, HR, and BP
- 2 patients developed ADE
  - Hyperamylasemia
  - Lung infiltration
  - Urine color change

## Purg, et al
- Single adult polypharmacy overdose
- $\geq 400$ mg citalopram
- Refractory status epilepticus
- QTc 570 msec, VT
- No ADE noted
- After infusing lipids
  - Resolution of seizures
  - Resolution of VT
  - Extubated 24 hours later

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Safety of SSRIs in Overdose

• Safer than TCA and MAOI in overdose
• Minimal interaction with other targets
• 15% develop serotonin syndrome
• 5% require mechanical intubation
• 2% develop seizures
Safety of SSRIs in Overdose

- Beaune, et al
  - Retrospective chart review of deliberate multi-drug overdoses
  - 148 exposed patients vs 296 controls
  - Serotonin syndrome underdiagnosed
  - No difference in arrhythmia (p=0.1)
  - Exposed had increased seizures (p=0.04)
  - Exposed had increased intubation (p=0.03)

SSRI Overdose Summary

- Manage by stopping serotonergic agents, giving benzodiazepines, and supportive care
- Treat seizures with high dose benzodiazepines
- Manage ECG changes with intravenous magnesium and sodium bicarbonate
- Minimal evidence supporting cyproheptadine use for serotonin syndrome
- No evidence to support intravenous lipids outside of polysubstance overdose
Patient Case Resolution

On hospital day 2 our patient is no longer showing signs of serotonin syndrome and is extubated without incident.

Later that day a repeat ECG demonstrates a QTc of 475 and our patient is subsequently discharged to the inpatient psychiatric unit. While recovering, a note is placed in her chart to avoid all serotonergic agents for several weeks.
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Definitions

Pharmacology: the study of drugs including their origin, composition, pharmacokinetics, and therapeutic use

Toxicology: the study of poisons, their detection, effects, and the methods of treatment for conditions they produce

Toxidrome: a specific constellation of symptoms associated with exposure to a given poison

I’ll be interested to see how you plan to transition into and out of this slide. I see what you’re doing by adding it, but I might ask you if it is necessary or if these points can be verbalized when they come up in your presentation. It’s all a flow thing, so both could be correct and once you describe in person your flow it will be more clear.

Scott D Nei, 9/19/2018
Cardiotoxicity in SSRI Overdose

- QRS widening
  - QRS >100 msec
  - Rare in SSRI overdose
  - Bind and alter sodium channel conformation
  - Altered channels impair myocardial conduction
    - Negative dromotropic
    - Negative inotropic
Miscellaneous SSRI Pearls and Toxicities

- Sertraline is most widely prescribed
- Citalopram and paroxetine most anticholinergic, sedating
- Paroxetine and fluvoxamine have no active metabolites
- Paroxetine highly associated with discontinuation syndrome
- Fluoxetine’s half-life precludes restarting antidepressants
- All SSRIs may inhibit platelet aggregation
- All SSRIs associated with SIADH
Background

- Selective serotonin reuptake inhibitors (SSRIs) are first line therapy for depression and anxiety
- Marketed in 1980’s for treatment of depression
- Use expanded to other neuro/psych disorders
- Safer than MAOI and TCA antidepressants
- Boxed warning for suicidality


SSRI Overdose Epidemiology

- 12% of American adults take antidepressants
- 4 of 5 take antidepressants long-term
- Antidepressant use increases with age
- Highest use in Whites, lowest in Asians
- 2:1 female to male ratio
- >52,000 SSRI overdoses annually
- >22,000 overdosed on SSRI alone
- Serotonin syndrome in ~15% of SSRI overdoses


So What to Do?

Fig. 5  QT nomogram

Heart Rate (bpm)

QT interval (msec)


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Mechanisms to Increase Serotonin

- Enhancing serotonin release
- Blocking serotonin reuptake
- Inhibiting serotonin metabolism
- Serotonin receptor agonism

# Serotonin Syndrome vs Neuroleptic Malignant Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Serotonin Syndrome</th>
<th>NMS</th>
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</thead>
<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td>Serotonergic drugs</td>
<td>Dopamine antagonists</td>
</tr>
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<td><strong>Onset</strong></td>
<td>Within 24 hours</td>
<td>Days to weeks</td>
</tr>
<tr>
<td><strong>Vitals</strong></td>
<td>Hyperthermia, hypertension, tachycardia, tachypnea</td>
<td>Hyperthermia, hypertension, tachycardia, tachypnea</td>
</tr>
<tr>
<td><strong>Mentation</strong></td>
<td>Agitation, coma</td>
<td>Stupor, alert mutism, coma</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Diaphoresis</td>
<td>Diaphoresis, pallor</td>
</tr>
<tr>
<td><strong>Muscles</strong></td>
<td>Hypertonia (especially in LE)</td>
<td>“Lead pipe” rigidity</td>
</tr>
<tr>
<td><strong>Reflexes</strong></td>
<td>Hyperreflexia, clonus</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td><strong>Pupils</strong></td>
<td>Mydriasis</td>
<td>Normal</td>
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<tr>
<td><strong>Bowels</strong></td>
<td>Hyperactive, N/V, diarrhea</td>
<td>Normal/hypoactive</td>
</tr>
<tr>
<td><strong>Recovery</strong></td>
<td>Usually within 24 hours</td>
<td>Up to 10 days</td>
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## Serotonergic Agents

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<thead>
<tr>
<th>Antidepressants</th>
<th>Drugs of abuse</th>
<th>Antiemetics</th>
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<tr>
<td>SSRIs</td>
<td>Amphetamines</td>
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<td>SNRIs</td>
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<td>TCAs</td>
<td>MDMA</td>
<td>Metoclopramide</td>
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<td>MAOIs</td>
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<td>Bupropion</td>
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<tr>
<td>Trazodone</td>
<td>St. John’s Wort</td>
<td>Dextromethorphan</td>
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<td><strong>Analgesics</strong></td>
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<td>Codeine</td>
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