

SEROTONIN SYNDROME IN CLOZAPINE WITHDRAWAL

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PRESENTATION OUTLINE

- Case Presentation**
- Clozapine**
- Clozapine withdrawal**
 - ✓ **Symptoms**
 - ✓ **Possibility of Serotonin syndrome**
- Teaching point**

CASE PRESENTATION

HPI: 60 year old male with HTN, HLD, hypothyroidism, self reported “manic depression” who presented from home after subacute fall with L foot pain and dizziness.

- Dizziness and weakness for 3 weeks, especially orthostatic
- Fell down in home, hit head, no LOC, down for 10 minutes
- L foot 10/10 pain for last 2 weeks, no inciting event remembered, sharp pain w/ movement and weight bearing

Vital Signs: BP 119/77, Pulse 82, Temp 97.9, RR 18, O2 100% (all within normal limits)

CASE PRESENTATION

Medications the patient reported as taking as of 12/29/2016:

- sertraline (ZOLOFT) 200 mg daily
- atenolol (TENORMIN) 25mg tab daily
- levothyroxine 137 mcg daily
- gabapentin (NEURONTIN) 800 mg daily qhs → HELD
- clonazepam (KLONOPIN) 0.25 mg BID prn → HELD

CASE PRESENTATION

Family History:

- Mother MI at age 70

Social History:

- Lives alone in hotel, has case manager who is his DPOA
- No contact with family
- Smoker 35 pack year, no alcohol last 10 years, uses marijuana daily

Assessment/Plan: Subacute metatarsal fracture, surgical repair when swelling reduced (2 weeks). Management of rhabdomyolysis (CK 1091) and leukocytosis (16.3).

CASE PRESENTATION

On Hospital Day 3

- **Depressed mood**
- **Suicidal ideation**
- **SI initially without plan, then to overdose on pills**

Hospital Day 4: Psychiatry consult placed

- **Continued to voice suicidal thoughts**
- **Less dizzy**
- **Tremors**
- **Diaphoresis**
- **Hypertension 144-171/78-89**
- **Tachycardia P89-104**

CASE PRESENTATION

Psychiatry Consultation

- Patient depressed, anxious over past several days due to being in the hospital, limited mobility, physical discomfort
- Patient had SI, but said he would not carry out plan

Psych History

- Psych medications: sertraline, clonazepam, and gabapentin
- Suicide attempt in the past with overdose of pills (10 yrs ago)
- One prior psych hospitalization
- Has seen outpatient psychiatrist for 5 years and has case manager

CASE PRESENTATION

Mental Status Exam

APPEARANCE: 60 YO male, appears older than stated age

BEHAVIOR: cooperative, psychomotor agitation, active movement of all extremities while lying down, tremulous

SPEECH: normal rate, tone, prosody

MOOD: "ok"

AFFECT: euthymic, reactive

THOUGHT PROCESS: linear, goal directed, future oriented

THOUGHT CONTENT: Reports vague SI without plan, denies HI, AH, VH, PI, IOR, not responding to internal stimuli

COGNITION: Orientedx4.

INSIGHT/ JUDGEMENT: fair/fair

CASE PRESENTATION

Assessment

- Suspected that SI in context of anxiety secondary to necessary medication changes in addition to overall adjustment associated with hospitalization and gait instability.

Plan

- Restart home medications gabapentin and klonopin due to concern for benzodiazepine withdrawal

CASE PRESENTATION

Hospital Day 5

Vitals: BPI 14-15 | 70-83, Pulse 90-107

- **Less tremulous, but shaking legs and raising arms involuntarily**
- **Less anxious since restarting clonazepam and gabapentin**
- **Difficulty sleeping (only 2 hours)**
- **Vague passive suicidal ideation without plan or intent**

CASE PRESENTATION

Hospital Day 6

Collateral from outpatient psychiatrist x5yrs

- *Schizophrenia*
- *Lithium, Perphenazine in past*
- *On Clozapine 300mg BID >5yrs*
- *Clozapine group every 2weeks*
- *Never known patient to be depressed*
- *Significant amount of anxiety*
- *Has been trying to titrate down gabapentin, clonazepam due to falls*

Vitals: BP 110-133/71-81, Pulse 62-78

- **Patient has not taken Clozapine for 6 days (medication from a different source/pharmacy)**
- **Possible cause/contributor of orthostasis and falls as outpatient**
- **Patient remembers taking clozapine when asked directly**
- **Denied history of AH, paranoia**

CASE PRESENTATION

Hospital Day 8-11

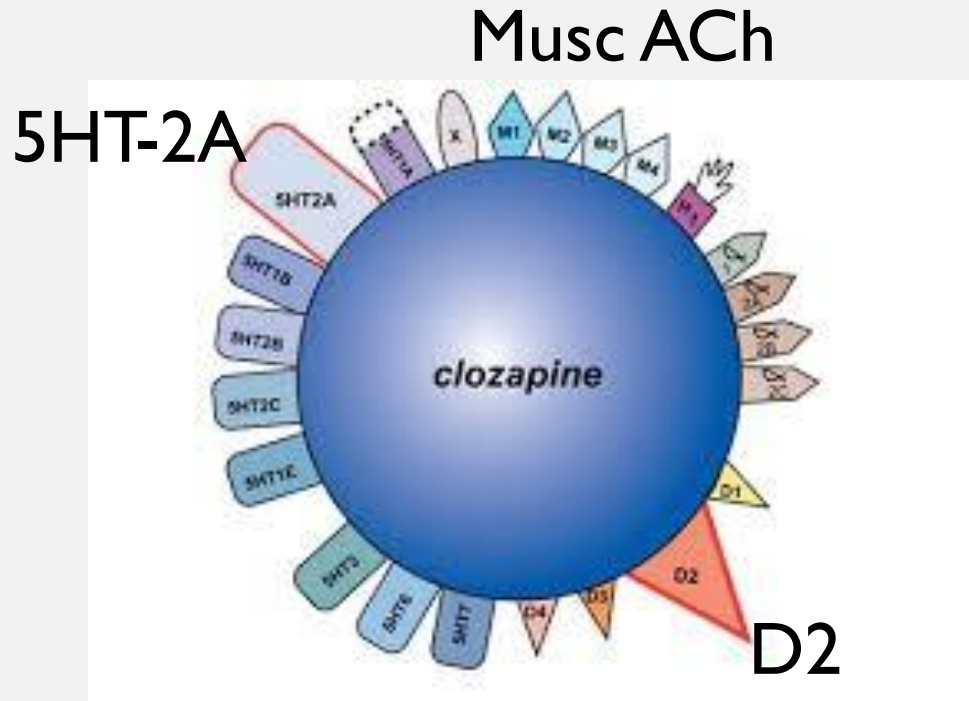
- **Restarted Clozapine at 12.5mg as >48hrs since last dose**
- **Patient continues to appear dysphoric, blunted affect with persistent suicidal ideation w/o plan, asked "Could you just kill me?"**
- **Denies AH, not internally preoccupied, not psychotic**
- **Neuro exam: Shaking less prominent today, involuntary arm movements much less today. 3+ reflexes throughout, tone normal.**
- **Discharged to Subacute Nursing Facility**

CLOZAPINE

- How was clozapine discovered?
- How does it work?
 - 5HT-2A partial antagonist
- When should it be prescribed?
- Clozapine initiation titration
- Monitoring
- Side effects

| Titration Schedule (example) | | | |
|------------------------------|--------------|-----------------|-----------------------|
| WEEK 1 | AM Dose (mg) | PM Dose (mg) | Total Daily Dose (mg) |
| Day 1 | 12.5 | 12.5 (optional) | 12.5–25 |
| Day 2 | 25 | --- | 25 |
| Day 3 | 25 | 25 | 50 |
| Day 4 | 25 | 50 | 75 |
| Day 5 | 50 | 50 | 100 |
| Day 6 | 50 | 75 | 125 |
| Day 7 | 50 | 100 | 150 |
| WEEK 2 | AM Dose (mg) | PM Dose (mg) | Total Daily Dose (mg) |
| Day 8 | 75 | 100 | 175 |
| Day 9 | 100 | 100 | 200 |
| Day 10 | 100 | 125 | 225 |
| Day 11 | 100 | 150 | 250 |
| Day 12 | 125 | 150 | 275 |
| Day 13 | 150 | 150 | 300 |
| Day 14 | 150 | 150 | 300 |

CLOZAPINE WITHDRAWAL



Clozapine has the highest affinity for acetylcholine receptors among the atypical antipsychotics

After chronic blockade of these receptors, they become upregulated and 'supersensitive', when the receptor blockade is withdrawn suddenly, the supersensitive receptors react excessively to acetylcholine

Clozapine withdrawal reactions (rebound)

1. Muscarinic (nausea, vomiting, delirium)
2. Dopaminergic (dystonias, dyskinesias, catatonia)

CLOZAPINE WITHDRAWAL

- Physical deterioration: delirium, vomiting, malaise, hyperreflexia
- “Cholinergic rebound,” including nausea, vomiting, hypersalivation, diarrhea, diaphoresis, insomnia, and agitation
- Elevated inflammatory markers (CRP, WBC), Elevated CK
- Rebound psychosis
- Catatonia (mutism, posturing, waxy flexibility, refusal to eat)
- Dystonia, dyskinesia
- Oculogyric crisis

Anticholinergics and olanzapine have been proposed as treatment options for preventing withdrawal when clozapine is discontinued acutely.

CLOZAPINE WITHDRAWAL

- 5HT2 antagonist
- There are case reports of abrupt clozapine withdrawal inducing serotonin syndrome with and without concomitant use of a serotonergic agent.
- Both acute and long-term clozapine use have been shown to downregulate the 5-HT 2A receptors in rat models
- Theorized that abrupt discontinuation of the drug removes antagonism and upregulation of the receptor
- Tx: cyproheptadine, anticholinergics



TEACHING POINTS

- **Clozapine is a D2 antagonist and 5HT2 antagonist**
- **Rebound psychosis and cholinergic symptoms most common in withdrawal**
- **Abrupt cessation leaves sensitized receptors open to available serotonin**
- **With continued use of SSRI upon discontinuation, possibility of inducing or worsening serotonin syndrome**

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