Recognizing Adverse Reactions with Psychotropic Drugs

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None to report
Objectives

✧ Identify serious adverse effects of psychotropic medications.
✧ Recognize risk factors for developing serious adverse events from psychotropic medication use.
✧ Recommend medication therapy management for a patient who has an identified adverse drug reaction to psychotropic medications.

Case Study:

✧ MB is a 47 year old male with schizoaffective disorder, recent pulmonary embolism, and chronic pain syndrome is admitted with worsening depression and suicidal ideation. Admit meds: lisinopril 20 mg daily, omeprazole 20 mg daily, warfarin 5 mg daily, hydrocodone/acetaminophen 5/325 mg q4h prn pain, olanzapine 30 mg hs, and citalopram 40 mg daily.
✧ Admitting MD changed olanzapine to 45 mg daily, citalopram to 60 mg daily, and started ETOH detox with chlordiazepoxide. He was given KCl 20mEq for a K⁺ of 3.2.
Case Study:

Day 2: A pain consult was ordered and omeprazole increased to 40 mg daily. Baseline EKG ordered due to citalopram 60 mg dose. QTc=402 msec

Day 3: Pain specialist stopped hydrocodone/acetaminophen and started methadone 10 mg bid and oxycodone IR 20 mg q6h prn BT pain. Attending decided to taper off of olanzapine and start clozapine titration.

Case Study:

Day 4: Patient overly sedated, methadone decreased to 5 mg bid and oxycodone IR to 5 mg q6h prn. Citalopram decreased to 40 mg daily and duloxetine 30 mg daily added.

Day 5: At 6:45 am patient was found unresponsive and CPR initiated. CPR was unsuccessful.

Autopsy reported that cause of death was inconclusive.
Discussion:

- Possible causes of death:
  - Pulmonary embolism?
  - Narcotic overdose/respiratory depression?
  - Drug/drug interaction?
  - Fatal arrhythmia?
  - Others?

- “When sudden death occurs without autopsy evidence for an explainable cause of death, an arrhythmic death is assumed.”


Torsade de pointes & QTc Prolongation
Torsade de pointes & QTc Prolongation

- Abnormally long QT interval when in normal sinus rhythm (as seen on ECG tracing)
- QT prolongation does not necessarily equate to development of Torsades de pointes
- Heart arrhythmia that produces no effective cardiac output (cardiac arrest)
- May last a few seconds resulting in lightheadedness, dizziness, palpitations, SOB
- If >10 seconds, patient collapses into unconsciousness and may develop seizure
- If it persists, death will result.

TdP Rhythm Strip
Torsade de pointes & QTc Prolongation

- Cardiac ion channels and proteins responsible for ventricular repolarization fail to work normally
- TdP frequently terminates spontaneously but may degenerate into ventricular fibrillation and sudden death
- Long QTc interval in post pubertal males is >470 msec and females is >480 msec.
- Each 10 msec increase in QTc contributes a 5-7% increase in risk for TdP
  - A patient with a QTc of 540 msec has a 63-97% higher risk for TdP than a patient with a QTc of 440 msec.
- No absolute threshold, but QTc > 500 msec is associated with 2- to 3-fold higher risk of TdP

Risk Factors for Torsades de pointes

- A QTc >500 msec (2-3 fold risk)
- Heart disease – congestive heart failure, myocardial infarct
- Bradycardia (esp. with premature beats)
- Renal or hepatic insufficiency
- Drug-drug interactions leading to increased blood levels
- Diuretic use
- Low serum potassium, calcium, or magnesium
- Female gender (2-fold risk)
- Congenital abnormalities of cardiac membrane ion channels
- Advanced age
- Use of more than one QTc-prolonging drug
- Clustering of multiple recognizable risk factors in a single patient
QTc Prolonging Medications

- Higher Risk Psych
  - Chlorpromazine
  - Citalopram
  - Droperidol
  - Eritoranem
  - Haloperidol
  - Pimozide
  - Thioridazine

- Higher Risk Non-Psych
  - Amiodarone
  - Azithromycin
  - Clarithromycin
  - Doxifluride
  - Erythromycin
  - Levofloxacin
  - Methadone
  - Mexiletine
  - Quinidine
  - Sotalol

- Possible Risk Psych
  - Aripiprazole
  - Clozapine
  - Risperidone
  - Lithium
  - Mirtazapine
  - Paliperidone
  - Quetiapine
  - Risperidone
  - Venlafaxine
  - Zyprexa

Case Review

- MB’s risk factors for TdP
  - Low serum potassium
  - Alcohol abuse, ? Hepatic insufficiency
  - No follow-up EKG
  - High risk medications
    - Citalopram 60 mg daily
    - Omeprazole 40 mg daily (increases citalopram concentration 120%)
    - Clozapine
    - Methadone
    - Olanzapine

www.crediblemeds.org/new-drug-list
Torsades: Reducing the Risk

- If efficacy is equal, a non-QT-prolonging agent is preferred.
- Who should get a baseline EKG?
  - Anyone with a history of cardiac arrest, blackouts, fainting, or seizures
  - Anyone with a family history of long QT syndrome, sudden death, or unexplained blackouts
  - Anyone with a risk factor who is starting a new drug known to prolong the QT
  - Initiation of a drug known to cause TdP
  - Severe hypokalemia or hypomagnesemia
- EKG should be repeated 8-12 hours after initiation or increased dose of QT-prolonging medications in at-risk patients.
  - At minimum check QTc at baseline, then recheck subsequent QTc interval when drug regimen reaches steady state.


Torsades: Prevention

- When QT interval of >500 msec or >60 msec over baseline is observed, promptly:
  - Discontinue potential contributing medications
  - Assess potentially aggravating risk factors and correct them (electrolytes, drug-drug interactions, etc.)
  - Have external defibrillator readily available
- Treatment of TdP: Magnesium sulfate 2 gm IV x 2
  - Nonsynchronized electric defibrillation if hemodynamically unstable
- Use www.crediblemeds.org/new-drug-list for updated list of QTc drugs
Case Study:

- 20 year old male presents to the ED complaining of being twitchy, muscle spasms, dizziness, and hot flashes. He states he is also having anxiety and racing thoughts. Currently he is taking citalopram 40 mg daily, buspirone 30 mg bid, trazodone 200 mg at bedtime, and desvenlafaxine 50 mg daily was just started two days ago. Vitals are temp 99.8, pulse 93, RR 20, BP 129/75. What is his diagnosis?

Serotonin Syndrome

- Triad of symptoms:
  - Mental status changes (anxiety, delirium, restlessness)
  - Autonomic hyperactivity (diaphoresis, tachycardia, hyperthermia, diarrhea)
  - Neuromuscular abnormalities (tremor, rigidity, myoclonus, hyperreflexia, diarrhea)
- Diagnosis made using Hunter Criteria: (one of the following)
  - Spontaneous clonus (i.e., involuntary rapid muscle contractions and relaxation)
  - Inducible clonus PLUS agitation or diaphoresis
  - Ocular clonus PLUS agitation or diaphoresis
  - Tremor PLUS hyperreflexia
  - Hypertonia PLUS temp > 38°C PLUS ocular clonus

Dunkley EJ. QJM 2003; 96:635.
Serotonin Syndrome

- Occurs when central and peripheral serotonin (5-HT$_{1A}$ and 5-HT$_{2A}$) receptors are over stimulated
- Due to medications and/or drugs of abuse
- Incidence is increasing due to the increasing use of serotonergic agents in medical practice.
- Incidence under-reported
  - Many clinicians unaware of the condition
  - Attribute to another cause
  - Dismiss mild cases

Onset

- Increased dose, overdose, drug-drug interaction, or addition of another serotonergic drug (esp. if different mechanism)
- 75% of patients have symptoms within 24 hours of precipitating event.
- Symptoms may be so mild they are ignored
- Presentation with fever and muscle rigidity should be considered a medical emergency!
  - Progression to multiorgan failure can occur within hours.
## Associated Medications

<table>
<thead>
<tr>
<th>Inhibition of serotonin reuptake:</th>
<th>Increased serotonin production:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenzaprine</td>
<td>L-tryptophan (a serotonin precursor)</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td></td>
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<tr>
<td>Meperidine</td>
<td></td>
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<tr>
<td>Methadone</td>
<td></td>
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<tr>
<td>SSRIs</td>
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<tr>
<td>St. John's wort</td>
<td></td>
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<tr>
<td>Tramadol</td>
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<tr>
<td>Trazodone</td>
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<tr>
<td>TCAs</td>
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<tr>
<td>Venlafaxine</td>
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</tbody>
</table>


## Associated Medications

<table>
<thead>
<tr>
<th>Inhibition of serotonin metabolism:</th>
<th>Increased serotonin release:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>Dextromethorphan</td>
</tr>
<tr>
<td>Phenytoine</td>
<td>Meperidine</td>
</tr>
<tr>
<td>Tranlycypromine</td>
<td>Methadone</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>MDMA (ecstasy)</td>
</tr>
<tr>
<td>Selegline</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
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<tr>
<td>Methylene blue</td>
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</table>

### Associated Medications

- **Stimulation of serotonin receptors:**
  - Buspirone
  - LSD
  - Meperidine
  - Lithium
  - Metoclopramide
  - DHE
  - Triptans

- **Cytochrome interactions:**
  - CYP2D6 inhibition
    - Bupropion doubles dextromethorphan levels
  - CYP3A4 inhibition
    - Diltiazem causes 5x increase in buspirone levels
  - CYP polymorphisms
    - 8% whites are CYP2D6 deficient


### Treatment

- **STOP THE OFFENDING AGENTS!**
- Supportive care (O₂, fluids, cardiac monitoring, etc.)
- Most cases resolve in 24 hours (depends on T₁/₂)
- Severe cases: diazepam 5 mg IV to reduce agitation, hypertonicity, hyperthermia, and neurologic excitability
  - Antipyretics not effective (fever is not centrally mediated)
- Some patients may need sedation, paralysis, and intubation
- Cyproheptadine 12 mg po stat then 2 mg q2h until symptoms resolve. Evidence of effectiveness lacking.
Reinitiation

- After adequate washout
- No increased risk
- Choose a less serotonergic medication
  - Bupropion, mirtazapine

Case Study

- 50 year old female with history of bipolar disorder attended a seminar seven days prior to admission and became delusional while there. She stopped drinking water because she thought the world was running out of water. Four days prior to admission she went to her psychiatrist, who changed her aripiprazole 7.5 mg daily to olanzapine 10 mg BID. One day prior to admission she showed signs of catatonia, elevated temp, and muscle stiffness. She was admitted with a temp of 101.9, WBC 14.8, CK 26,176, and myoglobin 13,770.
- Diagnosis?
Neuroleptic Malignant Syndrome (NMS)

◊ Tetrad of symptoms occur in virtually all cases:
  ◊ Mental status changes
  ◊ Muscular rigidity
  ◊ Hyperthermia
  ◊ Autonomic instability
  ◊ Evolves over days to weeks

NMS: Associated Medications

◊ All antipsychotics have been implicated
◊ Greatest risk with high-potency older antipsychotics (haloperidol, fluphenazine)
◊ Other dopamine modulating drugs like metoclopramide, promethazine, or recent stoppage of Parkinson’s disease medications
◊ Usually within 10 days of med change
NMS: Risk Factors

- High doses, rapid increases, switching meds, numerous IM injections
- Males > females
- Dehydration is present in 92% of cases
- Previous NMS episode
- Others: malnutrition, intense psychomotor excitement, physical exhaustion, organic brain disease

NMS: Pathogenesis

- Cause is unknown
- Incidence: 0.5-2.4%
- Hyperthermia and autonomic instability may be due to dopamine blockade in the hypothalamus
NMS: Diagnostic Criteria

- Essential Criteria – currently or recently on dopamine modulating drug
- Major Criteria – hyperthermia, “lead-pipe” rigidity, CK (3x normal or >1000 units/L)
- Minor Criteria – Altered mental status (AMS), EPS, marked autonomic instability, respiratory problems, leukocytosis (WBC>12000/mm³), low serum iron


NMS: Treatment

- **Stop the causative agent!**
- Supportive care in the ICU (fluids, cooling blankets, maintain cardiorespiratory stability)
- DVT prophylaxis
- Benzodiazepines to control agitation
- Bromocriptine (restores dopaminergic tone)
  - 2.5 mg po q6-8h x 10 days
- Dantrolene (skeletal muscle relaxant)
  - 1-2 mg/kg IV q6-12h x 10 days
  - Reduces heat production, rigidity, CK
- Electroconvulsive therapy
- Meds reduce recovery time (15 days vs. 9 days) and mortality (21% vs. 9%)
NMS: Prognosis

- Most episodes resolve within 14 days after stopping the causative drug (longer if long-acting injection)
- Mortality rate estimated to be 5-20%  
  - 38.5% in alcohol and drug addicts  
  - 4.4% if taking atypical antipsychotics  
- Patients with myoglobinemia and renal failure have a 50% mortality rate  
- Deaths usually due to cardiopulmonary arrest or myoglobinuric renal failure

NMS: Restarting Neuroleptics

- Risk factors for recurrence:  
  - Too early resumption of an antipsychotic  
  - Use of high-potency antipsychotic  
  - Injectable antipsychotic  
  - Concomitant use of lithium  

- If required:  
  - Wait at least 2 weeks after resolution  
  - Use lower potency antipsychotic  
  - Select drug from a different class of antipsychotic  
  - Start low dose and titrate slowly  
  - Avoid use of lithium  
  - Avoid dehydration  
  - Monitor for symptoms of NMS
# NMS vs. Serotonin Syndrome

<table>
<thead>
<tr>
<th><strong>Serotonin syndrome</strong></th>
<th><strong>NMS</strong></th>
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</thead>
<tbody>
<tr>
<td>Myoclonus (50%)</td>
<td>Lead-pipe muscle rigidity</td>
</tr>
<tr>
<td>AMS (agitation)</td>
<td>AMS (decreased level of consciousness)</td>
</tr>
<tr>
<td>Tremors (50%)</td>
<td>Mutism, stupor</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>WBC&gt;12000, CK&gt;1000</td>
</tr>
<tr>
<td>Shivering</td>
<td>Delayed onset (days)</td>
</tr>
<tr>
<td>Rapid onset (hours)</td>
<td>Hx dopaminergic agents</td>
</tr>
<tr>
<td>Hx serotonergic agents</td>
<td>Inc. temp</td>
</tr>
<tr>
<td>Inc. temp</td>
<td>EPS</td>
</tr>
<tr>
<td>Rambling speech</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Palpitations, tachycardia</td>
<td>Labile BP</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Diarrhea, nausea, vomiting</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Sialorrhea</td>
</tr>
</tbody>
</table>

## Clozapine: Case Study

- SR is a 15 year old female with schizophrenia with aggressive outbursts who failed trials of risperidone, aripiprazole, and quetiapine. A cross-titration with clozapine was initiated.

- Baseline WBC was 7.0 and ANC 4.8 but after 2 weeks of clozapine titration her WBC fell to 3.3 and ANC to 1.7.
Clozapine Monitoring Program

- Efficacy of clozapine
  - Reserved for patients who have failed treatment with standard antipsychotic medications (due to serious side effects)
- Adverse effects include agranulocytosis
  - Life-threatening reduction of infection-fighting WBCs (granulocytes)
  - Most cases occur with 4-10 weeks of initiation, cause unknown
- Clozapine "registries" created to ensure routine blood tests are being performed and monitored.
- CBC weekly for 6 months, q 2 weeks x 6 mo., then q 4 wks ad infinitum
- Acceptable WBC counts ≥ 3500/mm³ and ANC ≥ 2000/mm³

Clozapine Monitoring Program

- CBC is reported to the clozapine registry before the drug can be dispensed.
- If a substantial drop in WBC or ANC occurs:
  - Twice weekly CBC required until WBC > 3500/mm³ and ANC > 2000/mm³
  - Clozapine must be stopped if CBC does not improve.
  - Occasionally lithium or G-CSF is used to stimulate WBCs.
    - Lithium 300 mg/day added, in 2 weeks WBC 6.6 and ANC 3.9.
    - Consider later blood draw time (McKee 2011)
    - Increase in WBC by 667/mm³ and ANC by 1130/mm³
Hyponatremia: Case Study

❖ CW is a 56 year old female admitted with bipolar mania with psychosis. Her aripiprazole was changed to ziprasidone, topiramate was added as well as clonazepam and oxcarbazepine. After 10 days she began to complain of nausea and vomiting. Nurse states that the patient has already drank about 900 ml of water by 2 p.m.

❖ Her labs revealed a serum sodium of 120 mm/L (was 138 mm/L on admission).

Hyponatremia: Case Study

❖ Hospitalist ordered urine sodium, osmolality, instituted a 1500 ml fluid restriction, and stopped the oxcarbazepine.

❖ Urine sodium was 66 mm/L and osmolality 281 mOsm/kg

❖ Within 2 days the serum sodium was back to 134 mm/L and was feeling better physically
Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

SIADH

✧ Presentation:
  ✧ Nausea/vomiting, headache, confusion, fatigue, restlessness, weakness, seizures

✧ Labs:
  ✧ Hyponatremia (Na < 135 mm/L, urine osmolality > 100 mOsm/kg, urine Na > 40 mm/L

✧ Causes:
  ✧ Stroke, infection, trauma, psychosis
  ✧ Tumors esp. of lung, head, and neck; pulmonary diseases
  ✧ Psychotropic medications - Carbamazepine, oxcarbazepine, SSRIs, haloperidol, amitriptyline, MAOIs, opiates, valproic acid
SIADH

◊ Treatment:
  ◯ Stop the offending drug
  ◯ Institute fluid restriction of < 800 ml/day
    ◯ If not effective, administer sodium chloride orally or intravenously
    ◯ Caution – overly rapid correction can result in neurologic injury
      (keep < 10 mm/L per 24 hrs)
  ◯ Goal is serum sodium of 130 mm/L or higher
◊ Other considerations:
  ◯ Ecstasy intoxication
    ◯ Marked increase in fluid intake to avoid hyperthermia + SIADH
  ◯ Psychogenic polydipsia
  ◯ Excessive beer drinking
    ◯ Due to high carb & fluid intake without Na, K, or protein intake

Lithium: Case Study

◊ A 52 year old male bipolar patient being treated with lithium 450 mg po BID presents to the ED with dizziness, drowsiness, and worsening confusion. Coarse tremors were noted.

◊ A week earlier he was seen in the ED with complaints of neck & back pain and was given ketorolac 60 mg IM and discharged with a prescription for naproxen 500 mg po BID.

◊ Historically has had very stable lithium levels (0.8-1.0 mEq/ml).

◊ Li level 2.6 mEq/ml requiring emergent dialysis.
Lithium Toxicity

- Presentation:
  - Gastrointestinal – nausea, vomiting, diarrhea
  - Cardiac – rarely bradycardia & prolonged QTc
  - Neurologic – agitation, ataxia, confusion, sluggishness, neuromuscular excitability (coarse tremors, fasciculations, myoclonic jerks), slurred speech
- Differential Diagnosis:
  - Serotonin syndrome, NMS
- Toxic levels:
  - Therapeutic 0.8-1.2 mEq/L
  - Mild toxicity 1.5-2.5 mEq/L (tremor, slurred speech, lethargy)
  - Moderate toxicity 2.5-3.5 mEq/L (coarse tremors, clonus)
  - Severe toxicity >3.5 mEq/L (seizures, encephalopathy)

Lithium Toxicity

- Risk factors: Anything that affects kidney function – lithium excreted renally
  - Volume depletion, dehydration - GI losses, heart failure, cirrhosis, thiazide diuretics
  - Changes of renal function – NSAIDS, ACE inhibitors, ARBs
Lithium Toxicity

- **Treatment:**
  - Hydration – restoration of sodium and water balance in hypovolemic patients
  - Remove the interacting medications
  - Hemodialysis
    - If level > 4 mEq/L
    - If level > 2.5 mEq/L and patient has signs of significant toxicity (seizures, depressed mental status) or has an illness that would be exacerbated by aggressive hydration (e.g., CHF)
Lamotrigine: Case Study

- A 29 year old female with schizoaffective disorder arrives in ED with a severe generalized skin reaction (diffuse, erythematous, pruritic rash involving palms of hands and soles of feet). Four days prior she noticed a fever and bumps on her lips and oral mucosa. Meds include aripiprazole 30 mg po daily, citalopram 10 mg po daily, and lamotrigine 75 mg po daily (started 4 weeks ago).
Lamotrigine-Induced Stevens-Johnson Syndrome

✧ Presentation:
  ✧ Prodrome (1-3 days prior) of malaise and fever followed by:
  ✧ Rapid onset of erythematous rash, pruritic macules and plaques
  ✧ Skin lesions progress to epidermal necrosis and sloughing
  ✧ Mucous membranes almost always affected

✧ Risk factors:
  ✧ Co-administration with valproic acid
  ✧ Initial high doses or rapid dose titration
  ✧ Pediatric patients > adults
  ✧ Most cases occur in the first 8 weeks of treatment
  ✧ Asian ancestry with the HLA-B*1502 allele
Lamotrigine-Induced Stevens-Johnson Syndrome

- Treatment:
  - Stop lamotrigine at the first sign of rash!
  - Incidence of non-serious rashes is 7%, SJS 0.8%
  - Adult patients: High-dose, short term systemic steroids (e.g. prednisone or methylprednisolone), hydration
  - Pediatrics: IV immune globulin, hydration
  - Severe cases may require transfer to a burn unit
  - Sepsis is the major cause of death

Summary

- Psychotropic medications are widely used and relatively safe.
- Understanding risk factors is critical in preventing serious adverse reactions to psychotropic medications.
- Early recognition of signs and symptoms of adverse reactions is critical in providing essential treatment of serious adverse reactions to psychotropic medications.
References:


