Benzodiazepine-Induced Delirium
and Proton Pump Inhibitor Induced
Acute Renal Failure

BENZODIAZEPINE
(BZD) – INDUCED
DELIRIUM

Objectives

• Pharmacists
  o Describe the mechanism, presentation and management of benzodiazepine-induced delirium and proton pump inhibitor-induced acute renal failure
  o Recommend treatment plans for benzodiazepine-induced delirium and proton pump inhibitor-induced acute renal failure using case reports and series

• Pharmacy Technicians
  o Recognize the signs and symptoms of benzodiazepine-induced delirium and proton pump inhibitor-induced acute renal failure
  o List the treatment options for benzodiazepine-induced delirium and proton pump inhibitor-induced acute renal failure
**Epidemiology of Delirium**

- 14 – 24% of patients at hospital admission
- Up to 56% of hospitalized patients
- 32 – 67% undiagnosed cases
- 10 – 75% increased morbidity and mortality
- Most cases are multifactorial with polypharmacy
- 12 – 39% medication induced delirium
- Incidence of benzodiazepine induced delirium is unknown


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**Benzodiazepine Class Overview**

- Indications: anxiolytic, sedative, anticonvulsant, alcohol withdrawal, muscle relaxant
- Mechanism of action: binds to post-synaptic gamma-aminobutyric acid (GABA) receptor in CNS
- Contraindications: hypersensitivity drug or any component, acute narrow angle glaucoma, sleep apnea, severe respiratory insufficiency
- Warnings: anterograde amnesia, CNS depression, paradoxical reaction (hyperactive), hepatic impairment, CNS depression, withdrawal
- Monitoring: respiratory/CNS status, blood pressure, heart rate

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**Overview of Common Benzodiazepines**

<table>
<thead>
<tr>
<th></th>
<th>Dosing range (mg)</th>
<th>Peak plasma level (hr)</th>
<th>Metab/Elim</th>
<th>Elimination t ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 – 8 (IV)</td>
<td>2 - 4</td>
<td>urine, feces/ hepatic</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15 - 60</td>
<td>0.5 - 3</td>
<td>urine 80-90%/ hepatic</td>
<td>8 – 22</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125 – 0.5</td>
<td>0.5 – 2</td>
<td>urine/ extensively hepatic</td>
<td>2</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25 - 4</td>
<td>1 – 2</td>
<td>urine/hepatic</td>
<td>6.3 to 26.9</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.25 – 20 (IV)</td>
<td>0.5 – 1</td>
<td>urine, feces/ hepatic</td>
<td>1.8 - 6</td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25 - 20</td>
<td>1 - 4</td>
<td>urine/ extensively hepatic</td>
<td>18 - 50</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2 – 20 (IV)</td>
<td>1 – 2</td>
<td>Hepatic/renal as metabolites</td>
<td>20 - 100</td>
</tr>
</tbody>
</table>
DSM IV Definition: Substance-Induced Delirium

**Criterion**

- Disturbance of consciousness
- Change in cognition or perceptual disturbance
- Develops over a short period of time (hours to days) and fluctuates during the course of a day
- Evidence from history, physical exam, or lab findings that disturbance is caused by either (1) or (2):
  1. Symptoms in criteria A and B developed during substance intoxication
  2. Medication use is etiologically related to the disturbance

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**Presentation of Signs and Symptoms**

| Inability to focus, sustain, or shift attention | Misinterpretation |
| Memory impairment | Illusions |
| Disorientation | Hallucinations |
| Speech or language disturbance | Agitation |
| Sleep-wake cycle disturbance | Emotional disturbance (hypo/hyperactive) |
| Increased psychomotor activity | Rapid and unpredictable shifts in emotional states |
| Impaired judgment | |


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**Drug Induced Delirium**

| Anticholinergics (benztropine, atropine, scopalamine) | Antipsychotics (clozapine, haloperidol, olanzapine) |
| Anesthetics | Corticosteroid |
| Anticonvulsants (phenytoin, valproic acid, carbamazepine, levetiracetam) | Digoxin |
| Antidepressants (tricyclic antidepressants, lithium, bupropion) | H₂ receptor antagonists (cimetidine, ranitidine, famotidine) |
| Antiarrhythmics (amiodarone, lidocaine, quinidine) | Muscle relaxant (baclofen, cyclobenzaprine) |
| Antihistamines (diphenhydramine) | NSAIDs (diclofenac, ibuprofen, ketoprofen) |
| Antiparkinson agents (levodopa, bromocriptine, amantadine) | Opioids (fentanyl, meperidine, morphine) |
| Antispasmodics (oxybutynin) | Sedative Hypnotics (alcohol, barbiturates, BZD) |
Neurotransmitters in Delirium

- BZDs cause sedation, drowsiness, memory difficulties and lack of coordination and impaired learning of verbal and visual information
- Anterograde amnesia effects are greater following higher potency and shorter acting benzodiazepines
- Imbalance due to neurotransmitters
- BZD have high affinity to γ-aminobutyric acid in CNS which alter neurotransmitters
- Proposed mechanism of action involves dysfunction of GABA

Etiology of Benzodiazepine-Induced Delirium

- BZDs cause sedation, drowsiness, memory difficulties and lack of coordination and impaired learning of verbal and visual information
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Risk Factors

Patient
- Increased age
- Alcohol use
- Male
- Smoking
- Living alone

Environment
- Hospital admission
- Isolation
- No daylight
- No clock
- No visitors
- Noise
- ICU

More modifiable
- Acute Illness
- Length of stay
- Fever
- Lack of nutrition
- Hypotension
- Metabolic disorder
- Tubes/catheters
- Medications

Less modifiable
- Comorbidities
- Cardiac disease
- Cognitive impairment
- Pulmonary impairment
- Renal dysfunction

Van Rompaey B. Crit Care. 2009; 13:R77
### Medication Risk Factors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Transition to delirium only odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>1.2 (1.1–1.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.7 (0.9–3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.8 (0.9–3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.1 (0.9–1.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.4 (0.8–2.3)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Pandharipande P. Anesth 2006; 104: 21-6

### Sequelae of Delirium

- Increased mortality
- Increased length of stay
- Development of dementia
- Cognitive impairment
- Decreased functional abilities
- Increased need for chronic care
- Higher health care costs

Girard TD. Crit Care Med. 2010; 38: 1513-20
**Treatment Options**

- Recognition of offending agent
- Discontinue or reduce dose of possible offending agents
- Antidote if necessary
  - Flumazenil 0.2 mg iv
- Provide supportive care and orientation to environment
- Maintain competency
- Use of haloperidol or atypical antipsychotics if necessary
- Physostigmine 1-4 mg iv


**Case Report #1**

- CC: 63 y/o male presented to ED with complaint of intense sore throat, hoarseness, and dysphagia.
- PMH: diabetes, remote history of alcohol abuse
- VS: Temp: 38 C, Pulse: 122; BP: 106/68; RR: 22, O2%: 91
- Patient was given lorazepam 2 mg iv push for sedation for a procedure.
- ~ 25 min after administration, patient became abruptly agitated, flailing in bed, and uncooperative
- Vital Signs remained stable except HR: 105 beats/min
- Flumazenil 1 mg ivpush was administered with complete resolution of agitation within 1 min. Patient was cooperative and had no recall of procedure or episode


**Case Report #2**

- CC: 30 y/o male suffered 2nd and 3rd degree burns over 27% of total body surface area, mostly upper extremities, trunk and face but was not unconscious. Presented moderately anxious and apprehensive
- PMH: good health, history of histrionic personality disorder
- Medication: None
- Patient was admitted and placed on morphine drip. 3 days following admission, complained of increased pain and anxiety, lorazepam 2 mg iv was given, morphine was turned off 20 min later
- He awoke with complaints of pain during dressing change so morphine 5 mg iv was given but drip was still turned off. He did not recognize family, was fully disoriented with psychomotor agitation and unintelligible speech.

Case Report #2: Resolution

- Consciousness increased – able to recognize family and staff 5 hours after lorazepam dose but was still having persecutory delusions
- Patient was restarted on morphine iv drip, level of consciousness continued to improve.
- 7 hours after lorazepam injection, patient was fully awake, oriented, and responsive


Question 1

- Which of the following would be a treatment option for benzodiazepine induced delirium?
  - A. Antidote
  - B. Removal of agent
  - C. Antipsychotics
  - D. Maintain environment
  - E. All of the above

PROTON PUMP INHIBITOR (PPI) - INDUCED ACUTE INTERSTITIAL NEPHRITIS (AIN)
Acute Interstitial Nephritis:

Epidemiology

- 6 - 8% interstitial nephritides cause of acute renal failure cases
- 2 – 3% reported in renal biopsies
- 2/3 of cases are drug induced
- Other causes infectious (viral or bacterial)

Proton Pump Inhibitor Overview

- Indications: erosive esophagitis, gastroesophageal reflux disease, hypersecretory disorder, gastric ulcers, helicobacter pylori eradication
- Mechanism of action: suppression of gastric acid secretion by inhibiting H⁺/K⁺-ATPase in gastric parietal cell
- Contraindications: hypersensitivity to drug or any component
- Warnings: atrophic gastritis, carcinoma, fractures, gastrointestinal infections, severe hepatic impairment

<table>
<thead>
<tr>
<th>Proton Pump Inhibitor Overview</th>
<th>Dosage (mg/day)</th>
<th>T ½ life (hr)</th>
<th>Metabolism by CYP450 enzymes in the liver</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>15 – 30</td>
<td>1.5</td>
<td>75% = 80%</td>
<td>14 – 25% renal inactive metabolites, ≤1% parent drug in urine 67% bile</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40</td>
<td>1</td>
<td>CYP2C19 &gt; CYP2A6</td>
<td>71 – 82% renal inactive metabolites, no active drug in urine 18 – 20% fecal</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20</td>
<td>1 - 2</td>
<td>CYP2C19 &gt; CYP2A6</td>
<td>90% renal inactive metabolites, no active drug in urine 10% fecal</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20-40</td>
<td>0.5 - 1</td>
<td>CYP2C19 &gt; CYP2A6</td>
<td>77% renal inactive metabolites, &quot;minimal&quot; parent drug in urine 19% bile</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20-40</td>
<td>1 – 1.5</td>
<td>CYP2C19 &gt; CYP2A6</td>
<td>80% renal inactive metabolites, ≤1% parent drug in urine</td>
</tr>
</tbody>
</table>
Etiology: Acute Interstitial Nephritis

- Immune mediated tubulointerstitial injury
- Inflammation and edema of renal interstitium
- Infiltration of inflammatory cells within renal interstitium with edema sparing glomeruli and blood vessels
- Fibrotic lesions may be diffuse and patchy beginning in renal cortex
- Infiltrate composed of mononuclear cells and lymphocytes and eosinophils (may be absent)

Presentation of Signs and Symptoms

- Weakness
- Malaise
- Anorexia
- Fatigue
- Fever
- Rash
- Arthralgia
- Presents 7 days up to 9 months
  - Average 9.9 weeks after starting PPI
  - Rechallenge symptoms within days of exposure

Diagnosis

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Pyuria, hematuria, proteinuria, eosinophilia, urine sediment, WBC, WBC cast, RBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathology</td>
<td>Interstitial cellular infiltrate with or without tubulitis</td>
</tr>
<tr>
<td>Renal biopsy(Gold standard)</td>
<td>Eosinophilic cellular infiltrate</td>
</tr>
<tr>
<td>Lab findings</td>
<td>Elevation in creatinine or blood urea nitrogen occurs rapidly</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Fever, rash, eosinophilia, oliguria, arthralgia</td>
</tr>
</tbody>
</table>

Brewster UC. Clinical Nephrology, 2007 68(2):65-72
Overview of PPI-Induced AIN

- Idiosyncratic reaction
- Etiology remains unknown – most likely hypersensitivity immune reaction to drug or its metabolites
- Hypothesis: metabolites act as haptens (mimic renal antigens), planted antigens, circulating immune complexes


Drug-Induced Interstitial Nephritis

<table>
<thead>
<tr>
<th>Class of medications</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Cephalosporins, ciprofloxacin, ethambutol, isoniazid, macrolides, penicillins, rifampin, sulfonamides, tetracycline, vancomycin</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Furosemide, hydrochlorothiazide, triamterene</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Acyclovir, allopurinol, amiodipine, azathioprine, cephotaxim, carbamazepine, clofibrate, cocaine, creatine, diltiazem, famotidine, indinavir, mesalazine, phenytoin, prazosin, propylthiouracil, quinine, ranitidine</td>
</tr>
<tr>
<td>Other medications</td>
<td></td>
</tr>
</tbody>
</table>

Management

- Withdrawal of offending agent
- Corticosteroid
  - Prednisone 1 mg/kg for 1 – 2 months with rapid taper
- If no improvement consider
  - Dialysis
  - Mycophenalate mofetil

Brewster VC. Clinical Nephrology. 2007 68 (4):40-52
Sierra F. Alimentary pharmaol ther 2007. 26, 545 - 53
Case Report: PPI-Induced AIN

- CC: 36 yr old female admitted with 5 week history of nausea, vomiting and 7 kg weight loss, denied rash, arthralgia or fever but had chills
- PMH: cholecystectomy, hysterectomy, and arthroscopic knee surgery 8 wk before admission. Took omeprazole 20 mg daily for last 3 months for heartburn. Also took aspirin and APAP for migraines once a month. Last dose for migraine was a month ago and last dose for heartburn was 2 weeks prior to admission.
- Allergies: NKDA
- PE: afebrile, BP – 100/70 mmHg, rest of exam was unremarkable

Labs:
- Creatinine: 5.9 mg/dL
- Urinalysis: trace hematuria, proteinuria (660 mg/dL), pyuria, no RBC, cellular casts, or eosinophilia
- WBC, eosinophil, and platelet counts were WNL
- IV fluids administered but serum creatinine increased up to 7.68 mg/dL. Renal ultrasound showed bilateral renal enlargement with no evidence of obstruction
- A week later serum creatinine rose to 10.5 mg/dL so a renal biopsy was performed to reveal extensive interstitial infiltration of lymphocytes, plasma cells, eosinophils.
- Diagnosis of AIN due to omeprazole
- Prednisone 1 mg/kg was initiated
- Serum creatinine decreased to 8.92 mg/dL after 4 days and then returned to 1.26 mg/dL after 4 weeks

Case report (cont’d)

Labs:
- Creatinine: 5.9 mg/dL
- Urinalysis: trace hematuria, proteinuria (660 mg/dL), pyuria, no RBC, cellular casts, or eosinophilia
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PPI induced AIN : Case Series

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th>Baseline Cr (mg/dL)</th>
<th>Max Cr (mg/dL)</th>
<th>Tx at time of dx/duration</th>
<th>Tx after dx</th>
<th>F/U Cr/months post presentation</th>
<th>F/U eGFR (mL/min/1.73 m²)</th>
<th>Clinical Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>1.44</td>
<td>3.4</td>
<td>Omeprazole (3 wk)</td>
<td></td>
<td>2.04/12 months</td>
<td>34</td>
<td>Prolonged course of prednisone and azathioprine</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>1.02</td>
<td>3.06</td>
<td>Omeprazole (8 wk), felodipine (years), indapamide (2 yr), deer velvet (2 yr)</td>
<td></td>
<td>2.16/18 months</td>
<td>34</td>
<td>Incomplete recovery. Deer velvet (complementary therapy)</td>
</tr>
<tr>
<td>3</td>
<td>86</td>
<td>NA</td>
<td>8.18</td>
<td>Omeprazole (10 days), sotalol (yrs)</td>
<td></td>
<td>1.82/29 months</td>
<td>34</td>
<td>General aches, pains at presentation, dialysis (6 months)</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>1.02</td>
<td>2.84</td>
<td>Omeprazole (12 wk), bendrofluazide (yrs), atorvastatin (yrs), atenolol (yrs)</td>
<td></td>
<td>1.24/18 months</td>
<td>63</td>
<td>Presented with fever, polyuria, rechallenge with bendrofluazide no decline</td>
</tr>
<tr>
<td>5</td>
<td>82</td>
<td>1.02</td>
<td>3.63</td>
<td>Pantoprazole (months, intermittent)</td>
<td></td>
<td>1.93/36 months</td>
<td>34</td>
<td>PPI on irregular basis. Biopsy occasional eosinophil.</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>0.9</td>
<td>3.86</td>
<td>Omeprazole (6 months), ibuprofen, augmentin</td>
<td></td>
<td>1.02/24 months</td>
<td>67</td>
<td>Biopsy occasional eosinophil.</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>0.9</td>
<td>6.48</td>
<td>Omeprazole (5 mo), creatinine (mg/dL) (max), phosphorus (mg/dL) (max), hemoglobin (Hb) (max)</td>
<td></td>
<td>0.8/4 months</td>
<td>36</td>
<td>Presented with fever, rash, constipation, diarrhea, malaise, hematuria</td>
</tr>
</tbody>
</table>

References:
- Simpson IJ. Nephrology 2006; 11:381 - 85
## PPI induced AIN : Case Series

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th>Baseline Cr (mg/dL)</th>
<th>Max Cr (mg/dL)</th>
<th>Tx at time of dx/duration</th>
<th>F/U Cr/months post presentation</th>
<th>F/U eGFR (mL/min)</th>
<th>F/U</th>
<th>Clinical Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>84</td>
<td>0.95</td>
<td>2.4</td>
<td>Omeprazole (6 months), bendrofluazide (yrs), metoprolol and prednisone (6 months)</td>
<td>1.58/3 months</td>
<td>34</td>
<td>34</td>
<td>Fasting hyperglycemia, proteinuria for 4 months</td>
</tr>
<tr>
<td>10</td>
<td>78</td>
<td>1.25</td>
<td>4.2</td>
<td>Omeprazole (7 months), bendrofluazide (yrs), paroxetine (7 months), quinapril (yrs)</td>
<td>1.58/8 months, 1.36/12 months</td>
<td>41</td>
<td>41</td>
<td>Fasting hyperglycemia, hypothyroidism, labile hypertension, prednisone (6 months)</td>
</tr>
<tr>
<td>11</td>
<td>78</td>
<td>1.14</td>
<td>7.15</td>
<td>Omeprazole (18 months), recently doubled to 40 mg</td>
<td>1.33/18 months</td>
<td>41</td>
<td>41</td>
<td>Poor appetite, tired, unwell. No fever, polyuria, better after renal artery stent</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>1.02</td>
<td>4.65</td>
<td>Omeprazole 20 mg (8 months), metoprolol, diltiazem, doxazosin, simvastatin</td>
<td>2.04/10 months</td>
<td>26</td>
<td>26</td>
<td>Sudden decline in renal function, recovery after d/c PPI, no steroids</td>
</tr>
<tr>
<td>13</td>
<td>77</td>
<td>0.86</td>
<td>5.78</td>
<td>Omeprazole 20 mg (14 months), indapamide, methotrexate</td>
<td>1.53/3 months</td>
<td>86</td>
<td>86</td>
<td>Presented with chills, malaise, fatigue, methotrexate not cause</td>
</tr>
<tr>
<td>14</td>
<td>77</td>
<td>0.85</td>
<td>5.9</td>
<td>Omeprazole 40 mg (7 months, dose incr 3 months), candasartan, felodipine, metoprolol</td>
<td>1.53/3 Months</td>
<td>36</td>
<td>36</td>
<td>Anorexia, nausea, fatigue, eosinophils in biopsy - interstitial infiltrate, 2% WBC in urine sediment</td>
</tr>
</tbody>
</table>

## Question 2

All of the following statements are true regarding PPI induced AIN except:
- A. AIN is an immune mediated response
- B. AIN can present with anorexia and weakness.
- C. PPI induced AIN occurs in the first few days.
- D. The gold standard for diagnosis is a renal biopsy.
- E. Treatment of PPI induced AIN can include use of corticosteroids.