Drug Withdrawal Syndrome—Managing OUR drugs or THEIRS?

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Disclosure

Dr. Miller has no financial interests or arrangements that would be considered a conflict of interest.
Objectives

• Identify the mechanisms of pharmacologic dependence

• Recognize the signs and symptoms of drug cessation in relation to the withdrawal timeline

• Discuss management and treatment strategies of drug dependence

Overview

• Effects of withdrawal can be difficult to detect in critically ill patients

• Prevalence is not well defined in the inpatient setting

• Multimodal approaches may be warranted
Defining Dependence

- **Physical Dependence**: state of adaptation induced by repeated exposure to certain drug substances that is manifested by a *drug-or class-specific withdrawal syndrome* which is induced by abrupt cessation of exposure to the drug substance, a rapid dose reduction, a rapid decrease in blood level of the drug substance or its active metabolites, or by exposure to an antagonist.

Neurological Implications

- **Dopamine**: regulates mood, enhances pleasure, and is involved with movement, reward and reinforcing behaviors, and attention.

- **Serotonin**: stabilizes mood and regulates emotion.

- **Gamma-aminobutyric acid (GABA)**: mitigates stress response, lowers anxiety, slows down central nervous function.

- **Norepinephrine**: speeds up central nervous system, increases focus and attention while increasing energy levels.
Pathophysiology of Withdrawal

<table>
<thead>
<tr>
<th>Opioids</th>
<th>SSRIs/SNRIs</th>
<th>Benzodiazepines</th>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors: Mu, kappa, delta</td>
<td>Receptors: Neural serotonin or norepinephrine</td>
<td>Receptor: GABA&lt;sub&gt;A&lt;/sub&gt;</td>
<td>Receptors: D&lt;sub&gt;2&lt;/sub&gt; and 5-HT&lt;sub&gt;2A&lt;/sub&gt; (some histaminergic, cholinergic, and adrenergic)</td>
</tr>
<tr>
<td>• Locus coeruleus</td>
<td>• Neuronal adaptation (down-regulation)</td>
<td>• Pro-excitatory state</td>
<td>• Increased dopaminergic activity</td>
</tr>
<tr>
<td>• Upregulated cyclic adenosine monophosphate (cAMP)</td>
<td>• Change in neurotransmitter levels</td>
<td>• Activated dopaminergic neurons in ventral tegmental area</td>
<td>• Inhibition of release of acetylcholine and glutamate</td>
</tr>
</tbody>
</table>

The American Journal on Addictions 2019
New England Journal of Medicine 2017
CNS Drugs 2013
Severity and Duration of Withdrawal

• Depends on:
  – Length of exposure
  – Type of substance abused
  – Route of administration
  – Amount taken each time
  – Family history
  – Medical and mental health factors

Opioid Withdrawal Timeline

- Muscle aches
- Agitation and insomnia
- Tremor
- Sweats
- Hypertension
- Fever
- Nausea
- Vomiting
- Diarrhea
- Stomach cramping
- Depression

Onset: 6-48 hours  Peak: 3-10 days
Drug Half Lives: Opioids

<table>
<thead>
<tr>
<th></th>
<th>Immediate release</th>
<th>Extended release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>2-4 hours</td>
<td>8-24 hours</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2-3 hours</td>
<td>8-15 hours</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>3-4 hours</td>
<td>~5 hours</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2-3 hours</td>
<td>X</td>
</tr>
<tr>
<td>Codeine</td>
<td>3 hours</td>
<td>X</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>5 hours</td>
<td>X</td>
</tr>
<tr>
<td>Methadone</td>
<td>X</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

SSRI/SNRI Withdrawal Timeline

- **Sensory**
  - Paresthesia
  - Numbness
  - Shock-like
  - Rushing noise in head
  - Palinopsia
  - Light-headedness
  - Dizziness
  - Vertigo

- **Disequilibrium**
- **Somatic**
  - Headache
  - Tremor
  - Sweating

- **Affective**
  - Irritability
  - Anxiety/agitation
  - Low mood
  - Tearfulness

- **Gastrointestinal**
  - Nausea
  - Vomiting
  - Diarrhea

- **Sleep Disturbances**
  - Insomnia
  - Nightmares
  - Excessive dreaming

3-4 days

Symptoms can last from weeks to months
**SSRI/SNRI**

<table>
<thead>
<tr>
<th>SSRI</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Desvenlafaxine</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
</tr>
<tr>
<td>Vortioxetine</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
</tr>
</tbody>
</table>

*Most likely*  

*Least likely*

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**SSRI/SNRI Half Lives**

<table>
<thead>
<tr>
<th>Serotonin Reuptake Inhibitors</th>
<th>Serotonin and norepinephrine reuptake inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine 24 hours</td>
<td>Venlafaxine 5 hours</td>
</tr>
<tr>
<td>Sertraline 26 hours</td>
<td>Duloxetine 12 hours</td>
</tr>
<tr>
<td>Escitalopram 27-32 hours</td>
<td>Desvenlafaxine 12 hours</td>
</tr>
<tr>
<td>Citalopram 36 hours</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine 4-6 days</td>
<td></td>
</tr>
<tr>
<td>Vortioxetine 66 hours</td>
<td></td>
</tr>
</tbody>
</table>
Benzodiazepine Withdrawal Timeline

**Rebound**
- Anxiety
- Insomnia
- Panic attacks
- Headaches
- Hallucinations

**1-4 days**

**Full Withdrawal**
- Trembling
- Increased heart rate and blood pressure
- Nausea and vomiting
- Sweating
- Muscle spasms
- Seizures

**10-14 days**

**Return Anxiety**
- Hypersomnia
- Perceptual/cognitive impairments
- Irritability

**2 weeks**

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Benzodiazepine Half Lives

<table>
<thead>
<tr>
<th>Hypnotic</th>
<th>Anxiolytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>Diazepam</td>
</tr>
<tr>
<td>7-14 hours</td>
<td>24-48 hours</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>Chlordiazepoxide</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>6-38 hours</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>50 hours</td>
</tr>
<tr>
<td>2 hours</td>
<td>12-15 hours</td>
</tr>
</tbody>
</table>

Benzodiazepines with a shorter half-life are associated with a greater risk of dependence.
Antipsychotic Withdrawal Timeline

- Diaphoresis
- Headache
- Insomnia
- Restlessness
- Agitation
- Vertigo
- Alternating warmth and cold feelings
- Myalgias

1-4 days

2 weeks

Antipsychotic Half Lives

<table>
<thead>
<tr>
<th>Atypicals</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3-4 days</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12-66 hours</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>18-40 hours</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>30 hours</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1 day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>7 hours</td>
</tr>
</tbody>
</table>

| 1st Generation            |                  |
| Prochlorperazine          | 14-22 hours      |
| Haloperidol               | 14-37 hours      |
Strategies to Avoid Withdrawal and Rebound Syndromes

• Restart home medications
• Manage the acute phase
• Supportive measures

Treatment of Opioid Withdrawal

• Continue opioid agonist therapy
• Dose reduce/taper
• Non-opioid pharmacological options
  – Alpha$_2$ adrenergic agonists
  – Supportive cares
Objectives

Assess effectiveness of alpha\textsubscript{2}-adrenergic agonists compared with placebo, reducing doses of methadone, symptomatic medications for the acute phase of opioid withdrawal

Outcomes

Withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment

26 randomized controlled trials involving 1,728 participants

Non-Opioid Options: Gowing et al.

• Results:
  – Alpha\textsubscript{2} adrenergic agonists were more effective than placebo in severe withdrawal (RR 0.32, 95% CI 0.18 to 0.57)
  – Completion of treatment was significantly more likely compared to placebo (RR 1.95, 95% CI 1.34 to 3.84)
  – Clonidine and lofexidine are more effective than tizanidine and guanfacine compared to placebo
Treatment of Opioid Withdrawal: Alpha₂ agonists

<table>
<thead>
<tr>
<th>Clonidine (off label)</th>
<th>Lofexidine</th>
<th>Guanfacine</th>
<th>Tizanidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 to 0.2 mg every 6 to 8 hours</td>
<td>0.54 mg QID during peak withdrawal (continue up to 14 days)</td>
<td>No off-label use or consensus at this time</td>
<td></td>
</tr>
</tbody>
</table>

The American Journal on Addictions 2019

Treatment of Opioid Withdrawal: Supportive

- Sleep aids: low doses of trazadone or zolpidem
- Pain/muscle spasms: nonsteroidal anti-inflammatories, acetaminophen, cyclobenzaprine
- Nausea: ondansetron, metoclopramide, prochlorperazine
- Diarrhea: loperamide
- Anxiety: hydroxyzine or diphenhydramine
- Ensure adequate volume status

The American Journal on Addictions 2019
Opioid Conversion

Treatment of SSRI/SNRI Withdrawal

- Restart the medication at original dose

- Gradual tapering (2-6 weeks depending on dose)
  - Does not prevent onset of withdrawal phenomena
Treatment of Benzodiazapine Withdrawal

- Symptom-triggered approach
- Taper over a period of a few weeks to months
- Choose longer acting agent – diazepam
- Alternative medications – nonbenzodiazepine anxiolytic and hypnotic agents

New England Journal of Medicine 2017
Critical Care Clinics 2017

Non-benzodiazepine Alternatives:
Baandrup et al.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Assess benefits and harms of pharmacologic interventions to facilitate discontinuation of chronic benzodiazepine use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Randomized controlled trials comparing pharmacological treatment versus placebo or no intervention or versus another pharmacological intervention who had been treated with benzodiazepines for at least 2 months</td>
</tr>
</tbody>
</table>

Extracted data from 35 trials with 2,295 participants

Cochrane Database of Systematic Reviews 2018
Non-benzodiazepine Alternatives: Baandrup et al.

Results: Inconclusive

Use of beta blockers, antipsychotics, gabapentin, SSRIs, and antihistamines are not better than standard treatment

Treatment of Antipsychotic Withdrawal

• Continue or switch antipsychotic treatment

• 4 strategies when switching antipsychotic treatment
  – Plateau cross-taper switch
  – Abrupt switch
  – Ascending taper switch
  – Descending taper switch

• Agents to minimize withdrawal/rebound effects
  – Benzodiazepines, beta blockers, or anticholinergics
### Treatment of Antipsychotic Withdrawal

<table>
<thead>
<tr>
<th>Switching Strategy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch to Aripiprazole</strong> (from olanzapine, risperidone, or others)</td>
<td>Abrupt Descending taper Plateau cross-taper Good tolerability regardless of strategy (better with gradual discontinuation over 4-6 wks)</td>
</tr>
<tr>
<td><strong>Switch to Asenapine</strong></td>
<td>No switching trials available</td>
</tr>
<tr>
<td><strong>Switch to Iloperidone</strong></td>
<td>Abrupt Ascending taper Up-titration preferred due to risk of orthostatic hypotension</td>
</tr>
<tr>
<td><strong>Switch to Lurasidone</strong></td>
<td>No switching trials available</td>
</tr>
<tr>
<td><strong>Switch to Ziprasidone</strong> (from typicals, olanzapine, risperidone, or quetiapine)</td>
<td>Plateau cross taper switch Withdrawal or rebound phenomena usually not reported or discussed</td>
</tr>
</tbody>
</table>

### Treatment of Antipsychotic Withdrawal

<table>
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<th>Switching Strategy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch to Olanzapine</strong> (from clozapine, risperidone, or others)</td>
<td>Descending taper switch Plateau cross taper Good tolerance Clonidine – withdrawal dyskinesias and new onset headache</td>
</tr>
<tr>
<td><strong>Switch to Paliperidone</strong></td>
<td>Plateau cross taper Limited data – case reports only</td>
</tr>
<tr>
<td><strong>Switch to Quetiapine</strong> (from typical antipsychotics typicals, clozapine, or risperidone)</td>
<td>Plateau cross taper Improved extrapyramidal motor symptoms, but showed weight gain</td>
</tr>
</tbody>
</table>
Key Points

• Patients on therapy that alter neurochemistry are at risk for developing withdrawal syndrome

• Withdrawal severity and duration is determined by drug and patient factors

• Managing the acute phase of withdrawal is the most important step in patient care

References


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THANK YOU