Detection of iatrogenic opioid and benzodiazepine withdrawal in the ICU

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Disclaimers

• I’m an “adult-population ICU clinician”

• Received an investigator-initiated research grant form Pfizer
PAD and iatrogenic withdrawal

Tolerance

Delirium

Pain

Agitation, unpleasant awareness

Opioids

Sedatives

Iatrogenic Withdrawal

“Clinical syndrome after stopping, reducing or reversing a medication after prolonged exposure”

Epidemiology of IWS - Pediatric studies

• Incidence ranges from 9 to 87%

• Studies using a validated tool
  • 25 to 48% with the SOS
  • 37 to 77% with the WAT-1
  • 87% with the OBWS

Duceppe et al. PROSPERO CRD42016042746 (unpublished)
What about adults?

- In an ongoing SR on IWS, we screened 12923 citations and assessed 107 articles
- 48 articles included: 83% of studies in pediatrics

<table>
<thead>
<tr>
<th>Study types</th>
<th>Retrospective</th>
<th>Prospective</th>
<th>Randomized</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (n)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pediatric (n)</td>
<td>14</td>
<td>4</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>

Duceppe et al. PROSPERO CRD42016042746 (unpublished)
Epidemiology of IWS - Adult studies

- Mixed IWS rate of 31% and 32% in an RCT & a retrospective study, respectively

- Opioid withdrawal rate of 75% in one TBI study (n=40)

- HSCM and MGH
  - 1520 pts screened, 88 were eligible and 51 included
  - Opioid withdrawal of 16.7% (95%CI 6-27) in patients mechanically ventilated for > 72h

Cammarano et al Crit Care Med 1998;26::676-84
Wang et al. CCCF ePoster #83
Why so little data in adults?

- **IWS exists but a rare problem**
  - Age related
  - Shorter duration of sedatives/opioid use

- **IWS exists but identification is challenging**
  - Understanding the problem (triggers, symptoms, risk factors)
  - Screening tools
  - Overlap with other problems (agitation, pain, delirium, distress)
  - Unclear impact on outcomes
  - We don’t know how to manage IWS
Neonates, children and adults: all the same?

- Age-related differences in cellular mechanisms that mediate withdrawal
  - Changes in receptor populations
  - Ability of receptors to be internalized
  - Intracellular messengers
  - Transcription factors

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Adjusted ORs (95% CI)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age category</td>
<td></td>
<td></td>
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<tr>
<td>2 wk to 6 mo</td>
<td>2.73 (1.69–4.42)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 mo to 1.99 yr</td>
<td>1.55 (1.03–2.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>2.00–5.99 yr</td>
<td>1.20 (0.82–1.77)</td>
<td>0.34</td>
</tr>
<tr>
<td>6.00–17.99 yr</td>
<td>Reference</td>
<td>—</td>
</tr>
</tbody>
</table>

Barr et al. ILAR Journal 2011; 52:328-41
Best et al. Crit Care Med 2016 (ePub)
Shorter duration of sedatives/opioid use

- **Nursing-implemented sedation protocol** (Brook et al.)
  - Reduction in duration of MV (89.1 hours vs 124 hours)
- **Daily interruption of sedation infusions** (Kress et al.)
  - RR of extubation 1.9 (95%CI 1.3-2.7)
- **Paired sedation and ventilator weaning** (Girard et al.)
  - Increase in ventilator free days (14.7 vs 11.6 days; p=0.02)
- **Light versus deep sedation** (Treggiari et al.)
  - Increase in ventilator free days in first 7 days (6.6 vs 5.7 days)

Girard et al. Lancet 2008;371:126-34
Shorter duration of sedatives/opioid use

SCCM PAD guidelines:

- Recommend IV opioids to treat non-neuropathic pain in critically ill patients
- Suggest that nonopioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether)
- Favor light sedation with non-benzodiazepines

Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study

- 712 patients and 3620 patient-days
  - 176 patients with MV > 7 days (24.7%)

- Opioids were used in 84.8% of patients
  - Patients with MV > 7 days, mean daily dose of 113.4mg of morphine equivalents

- Benzodiazepines were used in 62.2% of patients
  - Patients with MV > 7 days, mean daily dose of 119.9mg of midazolam equivalents

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  - We don’t know how to manage IWS
Withdrawal triggers

- Abrupt cessation
- Rapid dose reduction
- Transition from IV to PO
- Alterations in GI absorption
- Delayed withdrawal
  - Organ dysfunction
  - Decreased drug clearance
  - Active metabolites
Signs and symptoms

• CNS stimulation
  • Agitation
  • Anxiety
  • Irritability
  • Restlessness
  • Pupillary dilatation
  • Sleep disturbances
  • Movement disorders
  • Increased muscle tone
  • Tremors
  • Hallucinations
  • Seizures

• Sympathetic system activation
  • Hypertension
  • Tachycardia
  • Tachypnea
  • Sweating
  • Fever

• GI disturbances
  • Nausea
  • Vomiting
  • Diarrhea

Risk factors in MV analysis

Pediatric population

- Hours of midazolam use (OR 1.05; 95%CI 1.02-1.10)
- **Number of days sedation** (OR 1.07; 95%CI 1.00-1.14)
- Number of days on ECMO (OR 2.40; 95%CI 1.10-5.30)
- Age (2-6 months > 6m-1.99 y > 2—5.99 > 6y-17.99)
- Mean daily opioid dose (OR 1.39; 95% CI 1.16-1.67)
- Cognitive impairment (OR 1.98; 95%CI 1.41-2.78)
- 3 or more sedative classes (OR 1.39; 95%CI 1.04-1.87)

Adult population

- **Dose of opioids** (OR 2.72; 95%CI 1,20-6,14)

Best et al. Crit Care Med 2016 (ePub)
Why so little data in adults?

- IWS exists but a rare problem
  - Age related
  - Shorter duration of sedatives/opioid use

- IWS has no impact on outcomes?

- IWS exists but identification is challenging
  - Understanding the phenomenon (triggers, symptoms, risk factors)
  - Screening tools
  - Overlap with other problems (agitation, pain, delirium, distress)
  - Unclear impact on outcomes
  - We don’t know how to manage IWS
DSM V criteria for opioid withdrawal

1. Presence of either cessation or reduction in opioid use that has been heavy and prolonged

2. Three or more of the following developing within minutes to several days following cessation or reduction:
   - Dysphoric mood
   - Nausea or vomiting
   - Muscle aches
   - Lacrimation or rhinorrhea
   - Pupillary dilatation
   - Piloerection
   - Sweating
   - Yawning
   - Fever
   - Insomnia

3. Causing distress and not explained by another phenomenon
DSM-V criteria for benzodiazepine withdrawal

A. Cessation of (or reduction in) sedative, hypnotic, or anxiolytic use that has been prolonged.

B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) sedative, hypnotic, or anxiolytic use:
   • 1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm)
   • 2. Transient visual, tactile, or auditory hallucinations or illusions
   • 3. Hand tremor
   • 4. Insomnia
   • 5. Nausea or vomiting
   • 6. Psychomotor agitation
   • 7. Anxiety
   • 8. Grand mal seizures

Detection of withdrawal

Opioid dependence related to substance abuse

• Clinical Opiate Withdrawal Scale (COWS)
• Clinical Institute Narcotic Assessment Scale (CINA)

Neonatal withdrawal

• Modified Narcotic Abstinence Scale or “Finnegan’s Scale”
Detection of iatrogenic withdrawal

• Pediatrics
  • Sedation Withdrawal Score
  • Opioid and Benzodiazepine Withdrawal Score (OBWS)
  • Withdrawal assessment tool (WAT-1)
  • Sophia Observation withdrawal Symptoms-scale (SOS)

• Adults
  • No validated scores
  • Studies have used adaptation of existing scores or specific symptoms
WAT-1 - Validation

Setting
• 215 PICU patients screened at 2 hospitals,
• 117 patients at risk of withdrawal
• 83 patients with withdrawal assessment data

Methods
• 19 of 21 symptoms of the “Opioid and Benzodiazepine Withdrawal Score”
• Symptoms with high redundancy or low levels of association with withdrawal intensity ratings were dropped
• 11-item (12-point) scale
• Standard: NRS 0-10 by the same nurse

Franck et al. Intensive and Critical Care Nursing 2004;20;344—351
• Score BID from weaning if opioids +/- or benzodiazepines by infusion or regular dosing for prolonged periods (e.g., > 5 days).

• Daily scoring until 72 hours after the last dose.

• 4 steps

• Positive score = 3 or greater

*Information from patient record, previous 12 hours*

<table>
<thead>
<tr>
<th>Any loose/watery stools</th>
<th>No = 0</th>
<th>Yes = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any vomiting/wretching/gagging</td>
<td>No = 0</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Temperature &gt; 37.8°C</td>
<td>No = 0</td>
<td>Yes = 1</td>
</tr>
</tbody>
</table>

*2 minute pre-stimulus observation*

<table>
<thead>
<tr>
<th>State</th>
<th>SBS¹ ≤ 0 or asleep/awake/calm = 0</th>
<th>SBS¹ &gt; +1 or awake/distressed = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>None/mild = 0</td>
<td>Moderate/severe = 1</td>
</tr>
<tr>
<td>Any sweating</td>
<td>No = 0</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Uncoordinated/repetitive movement</td>
<td>None/mild = 0</td>
<td>Moderate/severe = 1</td>
</tr>
<tr>
<td>Yawning or sneezing</td>
<td>None or 1 = 0</td>
<td>≥ 2 = 1</td>
</tr>
</tbody>
</table>

*1 minute stimulus observation*

| Startle to touch | None/mild = 0 | Moderate/severe = 1 |
| Muscle tone | Normal = 0 | Increased = 1 |

*Post-stimulus recovery*

| Time to gain calm state (SBS¹ ≤ 0) | < 2min = 0  | 2 - 5min = 1 | > 5 min = 2 |

*Total Score (0-12)*

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WAT-1 Validation

Results

• WAT-1 score of 3 had high sensitivity (0.87) and specificity (0.88)

• Predict nurses’ numeric rating scale (0–10) scores of >4

“No validation against a blinded clinician”
Sophia Observation withdrawal Symptoms-scale

Psychometric validation
• 154 children with continuous infusion of benzodiazepines and/or opioids for 5 or more days.
• Standard: NRS 0-10 by the same nurse
• Results:
  • Sensitivity and specificity were 0.83 and 0.93, respectively
  • Cutoff score of 4 or higher against a NRS score of 4 or higher

“No validation against a blinded clinician”

Sophia Observation withdrawal Symptoms-scale

• **Procedure**
  • Observation 3 times a day, at withdrawal suspicion and 2 hours after intervention

• **STEP 1**
  • Baseline values for heart and respiratory rates (mean over 24h)

• **STEP 2 - Evaluation of 15 symptoms**
  • **Autonomic dysfunction** (Tachycardia, Tachypnea, Fever, Sweating)
  • **Central nervous system** (Agitation, Anxiety, Tremors, Motor disturbances, Muscle tension, Inconsolable crying, Grimacing, Sleeplessness, Hallucinations)
  • **GI dysfunction** (Vomiting and diarrhea)

Evaluation in adults

Preliminary results

- 54 patients MV > 72h at HSCM and MGH
- WAT-1 compared to DSM V by an intensivist
- Assessments were blinded and performed independently
- The WAT-1 performed with a sensitivity of 50.0% (95% CI 21.5-78.5) and a specificity of 65.9% (95%CI 50.0-79.1)
- Item analysis

Martone et al. Unpublished
Impact of IWS

- Rouzé et al. (274 adult patients: 54 IWS vs 220 no IWS)
  - No differences in re-intubation, length of MV or duration of ICU stay

- Wanzuita et al.
  - 75 pts on fentanyl > 5 days randomized to methadone vs placebo
  - MV weaning time lower in the methadone group
Management

• Opioid and benzodiazepine weaning protocols
  • According to exposure (<7 days, 7-14 days and > 14 days)
  • 10-20% decrease every 24-48 hours
  • Rescue opioid available

• Transition to a longer-acting agent
  • Methadone

• Adjunctive medications
  • Clonidine and dexmedetomidine
  • Gabapentin

Galinkin & Koh. Pediatrics 2014;133:152
Conclusion

• IWS is infrequent in the general adult ICU population
  • Frequent in patients MV > 72-96hrs

• Need to rule out IWS in presence of agitation, pain, unpleasant awareness or delirium

• Outcomes data in adult and pediatric population is needed

• Need to study adults from the bedside
  • Behavioral symptoms and physiologic changes
  • Development of adapted screening tools

• Optimal weaning strategies remain to be identified
Questions
Pharmacology of opioid analgesia

- Opioid receptors are found in CNS as well as peripheral tissues
- Stimulated by endogenous peptides
- 3 types of receptors
  - Mu (μ) → Mu-1 (analgesia) and Mu-2 (respiratory depression, spinal analgesia and dependence)
  - Kappa (κ)
  - Delta (δ)

Tresco et al. Pain Physician 2008; 11:S133-S153
Opioid analgesia

Benzodiazepines

- Bind to a specific receptor site of the GABA receptor
- Produce dose-dependent respiratory depression
- Midazolam has active metabolites that accumulate in renal failure

Terms

• **Tolerance**
  • Decreased clinical effects after prolonged exposure

• **Withdrawal**
  • Clinical syndrome after stopping, reducing or reversing a medication after prolonged exposure

• **Dependence**
  • Physiologic and biochemical adaptation of neurons causing withdrawal or abstinence syndrome upon cessation

• **Tachyphylaxis**
  • Loss of drug effects caused by compensatory neurophysiologic mechanisms

• **Addiction**
  • Chronic syndrome of dependence and craving a drug for its euphoric or sedative properties