Management of Delirium in Hospice Patients

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Presentation Objectives

• Identify the clinical features of delirium
• Understand the underlying causes of delirium
• Compare and contrast between the medications that are commonly used to treat delirium in hospice care
**Definition of Delirium**

*Acute state* of mental confusion due to diffuse brain dysfunction characterized by cognitive failure

- Delirium is an urgent medical condition
- Delirium needs to be treated aggressively

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**Disease Burden**

- Cause significant distress
- Impairs communication
- Complicates assessment
  - pain & other symptoms
- Increases risk of falls/injuries
- Results in extended hospital stays
- Condition may be reversible
  - 1/2 of the cases

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**Prevalence**

50 – 75% of terminally ill patients

Delirium is a major cause of distress for:

- Patients
- Family
- Healthcare providers
Symptoms

- Hallucinations (visual, auditory, tactile)
- Delusions
- Confusion
- Agitation
- Tremor/myoclonus
- Insomnia or Sedation
- Withdrawal

Key Clinical Features

- Rapid onset: within hours or days
- Rapidly fluctuating course
- Reduced awareness of the environment
- Cognitive Impairment
- Behavior changes
- Emotional disturbances

Difficult to distinguish from dementia, depression and psychotic disorder except for the rapid onset and fluctuating course of symptoms

Categories

- Hyper-active
  - Confusion, Agitation, Aggression, Hallucinations, Myoclonus
  - Likely associated with drug use
- Hypo-active
  - Confusion, Sedation (rarely hallucinations or delusions)
  - Likely associated with dehydration and hepatic encephalopathy (difficult to detect)
  - Mistaken for depression (may mimic comatose state)
- Mixed
  - Patient may transition back and forth b/w above
Diagnostic Tools

<table>
<thead>
<tr>
<th>Nursing Delirium Screening Scale (NuDESC)</th>
<th>Mini Mental State Exam (MMSE)</th>
<th>Confusion Assessment Method (CAM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Tool</td>
<td>Assess cognition</td>
<td>Diagnostic only</td>
</tr>
<tr>
<td>Can be used to monitor delirium severity</td>
<td>Not specific for delirium</td>
<td>Does not assess severity</td>
</tr>
</tbody>
</table>

Possible Causes of Delirium

- Older age
- Dementia
- Depression
- Alcoholism
- Vision/Hearing Impairment
- Mobility Impairment
- Dehydration
- Bladder Catheterization
- Malnutrition
- Infection
- Poorly managed pain
- Polypharmacy
- Terminal illness

Who is at Greatest Risks?
Possible Causes at End of Life

- Pain
- Organ failure
- Infection
- Delirium
- Emotion Distress
- Dehydration
- Drug toxicity
- Hypoxia
- Electrolyte imbalance
- Infection
- Electrical imbalance
- Alcohol withdrawal

Drugs Causes Delirium

- Opioids
- Anticholinergic-type drugs
- Corticosteroids
- Benzodiazepines & sedative-hypnotics

Opioids Induced Neurotoxicity (OIN)

- OIN is a multifactorial syndrome that causes symptoms from mild confusion to hallucinations, delirium, and seizures
- All opioids may cause or contribute to delirium

Higher Risk
- Meperidine (highest risk)
- Hydromorphone

Lower Risk
- Fentanyl
- Methadone
Anticholinergics

- **Dose-dependent**
- **Additive toxicity from multiple drugs**

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Medication Examples (ABC score &gt;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antispasmodics (GI, GU)</td>
<td>Donnatal, Oxybutynin, Tolterodine, Dicyclomine</td>
</tr>
<tr>
<td>Antidepressants (older)</td>
<td>Amitriptyline, Nortriptyline, Paroxetine, Doxepin,</td>
</tr>
<tr>
<td>Drying Agents</td>
<td>Atropine, Scopolamine, Hyoscyamine</td>
</tr>
<tr>
<td>Antihistamines (older)</td>
<td>Diphenhydramine, Hydroxyzine, Meclazine</td>
</tr>
<tr>
<td>Muscle Relaxants</td>
<td>Methocarbamol, Cyclobenzaprine</td>
</tr>
<tr>
<td>Certain Antipsychotics*</td>
<td>Chlorpromazine, Olanzapine, Clozapine, Quetiapine</td>
</tr>
<tr>
<td>Antimuscarinics</td>
<td>Benztropine, Trihexyphenidyl</td>
</tr>
</tbody>
</table>

* Aging Brain Care Scale (ABC scale 2012)

Anticholinergic Burden

- **Direct effect** on CNS (confusion, agitation)
- **Indirect peripheral effects:**
  - Urinary retention
  - Blurred vision
  - Constipation
- Additive risk with multiple anticholinergics
- Geriatrics: increased sensitivity

*Hot – Dry – Mad*

Steroid Induced Psychosis

- **Common steroids**
  - Prednisone (Deltasone)
  - Dexamethasone (Decadron)
  - Methylprednisolone (Medrol)

- **Dexamethasone is preferred more often in palliative care**
  Prednisone 40mg = Dexamethasone 6mg

- **Risk of delirium** (The Boston Collaborative Drug Surveillance Study)

<table>
<thead>
<tr>
<th>Prednisone Dose</th>
<th>Dexamethasone Dose</th>
<th>Steroid Psychosis Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40mg/day</td>
<td>&lt;6mg/day</td>
<td>1.3%</td>
</tr>
<tr>
<td>40-80 mg/day</td>
<td>6-12mg/day</td>
<td>5% incidence</td>
</tr>
<tr>
<td>&gt;80mg/day</td>
<td>&gt;12mg/day</td>
<td>18%</td>
</tr>
</tbody>
</table>
Benzodiazepines

- Benzodiazepines may increase confusion & worsen delirium
- Long-acting versions more likely to accumulate to toxic level
- Limit benzodiazepines use to:
  - Hyperactive delirium not responding to antipsychotics
  - Delirium associated with alcohol or drug withdrawal
  - Intractable delirium where palliative sedation is indicated

<table>
<thead>
<tr>
<th>Long Acting</th>
<th>Short Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam (Valium)</td>
<td>Alprazolam (Xanax)</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>Lorazepam (Ativan)</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>Oxazepam (Serax)</td>
</tr>
</tbody>
</table>

Treatment Strategies

- TREAT underlying medical causes
- Treatment can improve/resolve delirium
- Improvement can occur even in last week of life
- Lack of intervention or treatment shown to have deleterious impact to the caregivers
Non-Pharmacological Approaches

- **Investigate possible causes**
- **Corrective action to address causes if possible**
- Create calm comfortable environment
- Provide orienting objects (clock, calendar)
- Have family members present
- Limit room & staff changes
- Allow for uninterrupted rest/sleep at night
- Consider 1 on 1 nursing/aide observation prn

Pharmacological Approach

Hyper-active Delirium
- Antipsychotics (drug of choice)
- Benzos (limited role)
- Re-hydration

Hypo-active Delirium (Depends on goals of tx)
- Non-sedating antipsychotic
- Stimulant therapy
- Re-hydration

Antipsychotics

**Drugs of Choice for the Treatment of Delirium**

- **Initial phase:**
  - Rapid dose titration to control symptoms Q1h prn
  - Titrate to effect within first 24h
- **Maintenance phase:**
  - 2/3 to 1/2 of the initial phase dose in 2 to 3 divided doses
  - Allow time to identify and/ or resolve delirium causes
- **Taper & D/C (if possible):**
  - Taper over 3 – 5 days if symptoms completely resolve

Innovation and Excellence in Advanced Illness at End of Life
Haloperidol (Haldol)

Most Preferred Antipsychotic for Delirium

- High potency
- Low sedative activity
- Low anticholinergic side effects
- Variety of dosage forms
  - Oral concentrate 2mg/ml
  - Injection solution 5mg/ml
  - Oral tablets: 0.5mg, 1mg, 2mg, 5mg, 10mg (crushable)
- Flexible route of administration (PO, SL, SC, IV)
- Most studied antipsychotic for delirium
- Lowest cost

Haloperidol Dosing

Aggressive approach (for severe agitation):
- **Adult**: 1mg Q6h **routine** & 2mg Q3h **prn**
- **Geriatric**: 0.5 - 1 mg Q6h **routine** & 0.5mg Q1h **prn**

Conservative approach:
- **Adult**: 1 - 2mg Q4 **prn**
- **Geriatric**: 0.25 - 0.5mg Q4h **prn**

Routes of administration: PO, SL, SC, IV

Caution for IV route (hypotension, cardiac toxicity)

(1) Dept of Palliative Care, MD Anderson Cancer Center
University of Texas
(2) American Psychiatric Association Guidelines

Efficacy of Antipsychotics

- **Conclusions** from a systematic review of pooled data from 3 large randomized, blinded studies:

  - **Haloperidol vs. Olanzapine & Risperidone for Delirium**:
    1. No difference in efficacy for delirium
    2. No difference in incidence of adverse effects **at low dosage**
    3. High dose Haloperidol was associated with increased **EPS**

  (Low dose Haloperidol defined: 4mg/day or less)
  (High dose Haloperidol defined: 5mg/day or greater)

Ref: Cochrane Database Syst Rev 2007 Apr 18 (2):CD005594
### Comparison of Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Usual daily adult dose (mg)</th>
<th>Side Effects</th>
<th>Sedation</th>
<th>EPS</th>
<th>Anticholinergic Effects</th>
<th>Orthostatic Hypotension</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>1 to 100</td>
<td>++ ++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>30 to 800</td>
<td>+++++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>4 to 16</td>
<td>++</td>
<td>0 to +</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Quetiapine*</td>
<td>50 to 800</td>
<td>++</td>
<td>0 to +</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Olanzapine*</td>
<td>5 to 20</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td></td>
</tr>
</tbody>
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*Atypical Antipsychotics
ESP = extrapyramidal side effects

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### Atypical Antipsychotics

- **Less EPS risk**
  - Parkinson’s disease
  - History of drug induced EPS
- **Less risk for QTc interval prolongation**
  - Cardiac disease
  - Bradycardia
  - Low potassium &/or magnesium levels

<table>
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<tr>
<th>Common Generic Atypicals Used for Delirium</th>
<th>Common Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone (Risperdal)</td>
<td>1mg BID</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>50mg BID</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>5 mg daily</td>
</tr>
</tbody>
</table>

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### Benzodiazepines

Benzodiazepines are used only:
- Palliative sedation (in severely agitated pt)
- Alcohol or sedative-drug withdrawal
- Lack of response to antipsychotics

Benzodiazepines may worsen delirium:
- Excessive sedation
- Increased confusion
- Ataxia
- Disinhibition (worsened hyperactivity)

Drugs: Lorazepam (Ativan), Alprazolam (Xanax), Clonazepam (Klonopin), Diazepam (Valium, Diastat), Midazolam (Versed)
Lorazepam (Ativan)

**Advantages**
- Prompt onset
- Short-acting
- Various dosage-forms: tablet, oral concentrate 2mg/ml, injection solution
- Inexpensive

**Initial Dosage**
- 0.5mg – 2mg Q 1 – 2 hours prn (PO, SL, IV)
- May use in combination with Haloperidol
  - increased sedation & decreased EPS potential

Palliative Sedation

- **Indications**
  - For severe hyperactive delirium
  - Terminal patients
  - Not responding to antipsychotics
- Treatment can be used with antipsychotic or alone for palliative sedation:
  - Benzos: Lorazepam or Midazolam (PO, SL, SC, IM, IV)
  - Phenobarbital (PO, rectal, SC, IV)

Examples of starting dose:
- Midazolam (Versed) 0.5-1mg/hr infusion IV or SC
- Phenobarbital 100mg rectal Q8-12 hr

Stimulant Therapy

- **Treatment option for hypo-active delirium**
- **Goal of maximize alertness & ability to interact**
- Methylphenidate (off label use)
  - 10mg to 60mg/day in 1 or 2 divided doses
  - Limited evidence to guide therapy
  - Associated with significant risks for terminal patients
    - hallucinations, agitation, tachycardia
Re-hydration

- Oral, IV, SC
- IV/SL re-hydration may prolong life
  - May not align with the goals of therapy for terminal patients
- Risks of worsening dyspnea or edema
  - CHF
  - Renal impairment

Summary

- Delirium is common in palliative care patients
- Treatment focus on finding the cause and symptom control
- Always review the patient’s medication regimen
- Ensure adequate pain control
- Prompt control of agitation in delirium is essential
- Primary drug for agitation is haloperidol
- Benzodiazepines has limited role
- Atypical antipsychotics are for patients at high risk for EPS