**BACKGROUND**

- Known by multiple names: acute confusional state, acute mental status change, organic brain syndrome, reversible dementia, toxic or metabolic encephalopathy
- Predictor for future cognitive and functional decline as well as diminished lifespan
- Found in 1/3 of hospitalized medical patients over age 70
- Found in 1/3 of patients over age 70 presenting to emergency department
- Under-recognized: only 20% of cases recognized by physicians; only 50% by nurses
- Failure to diagnose/manage delirium leads to costly, life-threatening complications; loss of function, independence

**DIFFERENTIAL DIAGNOSIS**

- **NOTE:** The concept of “differential diagnosis of delirium/dementia/depression” can be misleading—*conditions may coexist and are risk factors for one another*

**HPI**

- DSM-IV-TR criteria, although precise, are difficult to apply; therefore, Confusion Assessment Method (CAM) is preferred
- CAM-ICU is a variant of the CAM and does not require verbal responses from the patient

### DSM IV-TR Criteria vs. Confusion Assessment Method (CAM) Diagnosis

<table>
<thead>
<tr>
<th>DSM IV-TR Criteria</th>
<th>Confusion Assessment Method (CAM) Diagnosis requires: #1 and #2 and either #3 or #4:</th>
</tr>
</thead>
</table>
| Disturbance of consciousness with reduced ability to focus, sustain, or shift attention | 1. Acute change in mental status and fluctuating course:  
- Is there evidence of an acute change in cognition from the patient's baseline? 
- Does the abnormal behavior fluctuate during the day (tend to come and go, or increase or decrease in severity)? |
| A change in cognition (memory, orientation, language, etc.) or the development of a perceptual disturbance (hallucinations, etc.) that is not better accounted for by a preexisting, established, or evolving dementia | 2. Inattention:  
- Does the patient have difficulty focusing attention?  
- Can use one of the following tests for attention:  
  - Digit span  
  - Days, months  
  - Continuous performance task  
  - Serial 7's  
  - “World” backward |
| Disturbance develops over a short period of time (hours to days) and tends to fluctuate during course of the day | 3. Disorganized thinking:  
- Is the patient's thinking disorganized or incoherent (rambling or irrelevant conversation, unclear or illogical flow of ideas, unpredictable switching from subject to subject)? |
| History, physical exam, or lab findings provide evidence that the disturbance is caused by the direct physiologic consequences of a general medical condition, a drug, or both | 4. Altered level of consciousness:  
- Is the patient's mental status anything other than alert (vigilant, lethargic, stuporous, comatose)? |

**PREDISPOSING AND PRECIPITATING FACTORS**

- As the number of predisposing factors for delirium increase, a decreased number of precipitating factors are required to initiate delirium
- **Predisposing factors:** advanced age, dementia, prior delirium, dependency in activities of daily living (ADLs), medical comorbidities, history of alcohol abuse, male gender, diminished vision and/or hearing

<table>
<thead>
<tr>
<th>Precipitating Factors (Mnemonic for Causes of Delirium)</th>
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</table>
| **Drugs**  
- Any new additions, increased dosages, or interactions  
- Consider over-the-counter drugs and alcohol  
- Consider especially high-risk drugs (see "Medications," next page) |
| **Electrolyte disturbances**  
- Especially dehydration, sodium imbalance  
- Thyroid abnormalities |
| **Lack of drugs**  
- Withdrawal from chronically used sedatives, including alcohol and sleeping pills  
- Uncontrolled pain |
| **Infection**  
- Especially respiratory, skin, and urinary tract infections |
| **Reduced sensory input or mobility**  
- Poor vision, poor hearing  
- Use of restraints, bedbound status |
| **Intracranial**  
- Rare: consider only if there are new focal neurologic findings or suggestive history, or diagnostic evaluation is otherwise negative  
- Infection, hemorrhage, tumor, stroke |
| **Urinary, fecal**  
- Urinary retention ("cystocerebral syndrome")  
- Fecal impaction  
- Urinary catheterization |
| **Myocardial, pulmonary**  
- Myocardial infarction, arrhythmia, exacerbations of congestive heart failure or chronic obstructive pulmonary disorder, hypoxia |
| **Surgery**  
- Incidence of delirium:  
- 15% after elective noncardiac surgery  
- Up to 50% after cardiac bypass, abdominal aortic aneurysm (AAA) or hip fracture repair |
PHYSICAL EXAM
- Vital signs, including oxygen saturation
- Thorough physical exam with focus on neurologic and mental status examination

MEDICATIONS
- Alcohol; anticholinergics (oxybutynin, benztropine); anticonvulsants (primidone, phenobarbital phenytoin); antidepressants (amitriptyline, imipramine, doxepin); antihistamines (diphenhydramine); anti-inflammatory agents (prednisone); antiparkinsonian agents (levodopa-carbidopa, dopamine agonists, amantadine); antipsychotics; barbiturates; benzodiazepines (triazolam, alprazolam, diazepam, flurazepam, chlordiazepoxide); H2 antagonists (cimetidine, ranitidine); opioid analgesics (especially meperidine)

LABS
- Based on history and physical:
  - Complete blood count
  - Thyroid function test
  - Serum drug levels
  - Chest x-ray
  - Cerebral imaging rarely helpful, except with head trauma or new focal neurologic findings
  - Electroencephalogram and cerebrospinal fluid analysis rarely helpful, except with associated seizure activity or signs of meningitis

MANAGEMENT PRINCIPLES
- Prevention is superior to management
- Requires interdisciplinary effort by physicians, nurses, family, others
- Multifactorial approach is most successful because multiple factors contribute to delirium

MANAGEMENT STRATEGIES
<table>
<thead>
<tr>
<th>STEP</th>
<th>KEY ISSUES</th>
<th>PROPOSED TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identify and treat reversible contributors</td>
<td>Medications</td>
<td>Reduce or eliminate offending medications, or substitute less psychoactive medications</td>
</tr>
<tr>
<td></td>
<td>Infections</td>
<td>Treat common infections: urinary, respiratory, soft tissue</td>
</tr>
<tr>
<td></td>
<td>Fluid balance disorders</td>
<td>Assess and treat dehydration, heart failure, electrolyte disorders</td>
</tr>
<tr>
<td></td>
<td>Impaired central nervous system oxygenation</td>
<td>Treat severe anemia (transfusion), hypoxia, hypotension</td>
</tr>
<tr>
<td></td>
<td>Severe pain</td>
<td>Assess and treat; use local measures and scheduled pain regimens that minimize opioids; avoid meperidine</td>
</tr>
<tr>
<td></td>
<td>Sensory deprivation</td>
<td>Use eyeglasses, hearing aid, portable amplifier; clear cerumen</td>
</tr>
<tr>
<td></td>
<td>Elimination problems</td>
<td>Assess and treat urinary retention and fecal impaction</td>
</tr>
<tr>
<td>2. Maintain behavioral control</td>
<td>Behavioral interventions</td>
<td>Teach hospital staff appropriate interaction with delirious patients; encourage family visitations</td>
</tr>
<tr>
<td></td>
<td>Pharmacologic interventions</td>
<td>If necessary (see Pharmacologic Therapy of Agitated Delirium)</td>
</tr>
<tr>
<td>3. Anticipate and prevent or manage complications</td>
<td>Urinary incontinence</td>
<td>Implement scheduled toileting program</td>
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<tr>
<td></td>
<td>Immobility and falls</td>
<td>Avoid physical restraints; mobilize with assistance; use physical therapy</td>
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<tr>
<td></td>
<td>Pressure ulcers</td>
<td>Mobilize; reposition immobilized patient frequently and monitor pressure points</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance</td>
<td>Implement a nonpharmacologic sleep protocol; avoid sedatives</td>
</tr>
<tr>
<td></td>
<td>Feeding disorders</td>
<td>Assist with feeding; use aspiration precautions; provide nutritional supplementation as necessary</td>
</tr>
<tr>
<td>4. Restore function in delirious patients</td>
<td>Hospital environment</td>
<td>Reduce clutter and noise (especially at night); provide adequate lighting; have familiar objects brought from home</td>
</tr>
<tr>
<td></td>
<td>Cognitive reconditioning</td>
<td>Have staff reorient patient to time, place, person at least three times daily</td>
</tr>
<tr>
<td></td>
<td>Ability to perform ADLs</td>
<td>As delirium clears, match performance to ability</td>
</tr>
<tr>
<td></td>
<td>Family education/support/participation</td>
<td>Provide education about delirium, its causes and reversibility, how to interact, and family’s role in restoring function</td>
</tr>
<tr>
<td></td>
<td>Discharge</td>
<td>Because delirium can persist, provide for increased ADL support; follow mental status changes as “barometer” of recovery</td>
</tr>
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PHARMACOLOGICAL THERAPY OF AGITATED DELIRIUM

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Benefits</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Antipsychotic</td>
<td>0.25–1 mg po or IM q4h prn agitation</td>
<td>Relatively nonsedating; few hemodynamic effects</td>
<td>EPS, especially if &gt;3 mg/d</td>
<td>Usually agent of choice&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Olanzapine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Antipsychotic</td>
<td>2.5–5 mg po or IM q24h, max dosage 20 mg q24h (cannot be given by IV infusion)</td>
<td>Fewer EPS than haloperidol</td>
<td>More sedating than haloperidol</td>
<td>Small case series only&lt;sup&gt;5&lt;/sup&gt;; oral formulations less effective for acute management</td>
</tr>
<tr>
<td>Quetiapine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Antipsychotic</td>
<td>25–50 mg po q12h</td>
<td>Fewer EPS than haloperidol</td>
<td>More sedating than haloperidol; hypotension</td>
<td>Small case series&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td>Risperidone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Antipsychotic</td>
<td>0.25–1 mg po or IV q4h prn agitation</td>
<td>Similar to haloperidol</td>
<td>Might have slightly fewer EPS</td>
<td>Case series only&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lorazepam&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Sedative</td>
<td>0.25–1 mg po or IV q8h prn agitation</td>
<td>Use in sedative and alcohol withdrawal, and history of neuroleptic malignant syndrome</td>
<td>More paradoxic excitation, respiratory depression than haloperidol</td>
<td>Second-line agent, except in specific cases noted</td>
</tr>
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NOTE: EPS = extrapyramidal symptoms; OL = off-label use

<sup>4</sup>In a randomized trial comparing haloperidol, chlorpromazine, and lorazepam in the treatment of agitated delirium in young patients with AIDS, all were found to be equally effective, but haloperidol had the fewest adverse events.

<sup>5</sup>The FDA has attached warnings to the second-generation antipsychotics because of the increased risk of stroke and mortality associated with their long-term use, primarily for agitation in dementia.

FOLLOW-UP
- Symptoms of delirium may persist for weeks to months
- An episode of delirium is a risk factor for subsequent episodes; documentation is critical
- A history of delirium is a risk factor for dementia: education and follow-up are important
### Absorption
Rate and extent are usually unaffected

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<th>AGE EFFECT</th>
<th>DISEASE, FACTOR EFFECT</th>
<th>PRESCRIBING IMPLICATIONS</th>
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<td>Absorption</td>
<td></td>
<td>Achlorhydria, concurrent medications, tube feedings</td>
<td>Drug-drug and drug-food interactions are more likely to alter absorption</td>
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<td>Distribution</td>
<td>Increase in fat:water ratio; decreased plasma protein, particularly albumin</td>
<td>Heart failure, ascites, and other conditions increase body water</td>
<td>Fat-soluble drugs have a larger volume of distribution; highly protein-bound drugs have a greater (active) free concentration</td>
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<td>Metabolism</td>
<td>Decreases in liver mass and liver blood flow decrease drug clearance; may be age-related changes in CYP2C19, while CYP3A4 and 2D6 are not affected</td>
<td>Smoking, genotype, other medications, alcohol, and caffeine have more effect than aging on metabolism</td>
<td>Lower dosages may be therapeutic</td>
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#### Sentinel event that should trigger consideration to stop one or more medications:
- Care transitions
- Annual/semiannual medications review
- Starting a new medication
- New problem

#### Educate patient and/or caregiver regarding:
- What to expect/intent of stopping medications
- Instructions, eg, how to taper (if indicated)
- Monitoring and follow-up:
  - Withdrawal reactions
  - Exacerbation of underlying conditions

### Distribution
Increase in fat:water ratio; decreased plasma protein, particularly albumin

#### Precisely:
- Write legibly
- Write out the directions, strength, route, quantity, and number of refills
- Always precede a decimal expression of <1 with a zero (eg, 0.01); never use a zero as the final digit after a decimal
- Avoid using abbreviations, especially easily confused ones (eg, qd and qid)
- Avoid brand names
- Do not use ambiguous directions such as “as directed” or “as needed”
- Include the medication’s indication in the directions
- Write dosages for thyroid replacement therapy in mcg, not mg
- E-prescribe when possible
- Always re-read what you’ve written

### Approach to Reducing Medication Errors
- Know, or identify a real-time resource for understanding, a medication’s:
  - Dose range
  - Common adverse events
  - Potential for drug-drug interactions
  - Potential for drug-nutrient interactions
  - Potential for drug-disease interactions

### Age-Associated Changes in Pharmacokinetics and Pharmacodynamics

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<td>Elimination</td>
<td>Primarily renal; age-related decrease in glomerular filtration rate</td>
<td>Kidney impairment with acute and chronic diseases; decreased muscle mass results in less creatinine (Cr) production</td>
<td>Serum Cr not a reliable measure of kidney function; best to estimate Cr clearance using formula</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>Less predictable and often altered drug response at usual or lower concentrations</td>
<td>Drug-drug and drug-disease interactions may alter responses</td>
<td>Prolonged pain relief with opioids at lower dosages; more sedation and postural instability from benzodiazepines; altered sensitivity to beta-blockers</td>
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