Delirium Management in 2018

“What do you mean Haldol doesn’t work?”

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Delirium

de = off
lira = furrowed field
“off the track”

What we’ll do

- Describe delirium so you can recognize it more easily
- Causes and physiology
- Interventions
  - Environment
  - Drugs
  - Caregivers
- New evidence from publications in 2017
Disclosure #1

- While some of this talk is about medicines for delirium, most of delirium management boils down to:
  - Recognizing it
  - How we talk about it
  - How we manage expectations
- I have no financial relationships to disclose regarding this material

Disclosure #2

Often makes you feel powerless

Difficult, potentially dangerous to ignore
Delirium

- Acute Confusional State
  - Altered level of consciousness
  - Inattention
  - Disordered thinking
  - Increased (agitated) or decreased (hypopactive) psychomotor activity
- Waxing/waning course
- “Brain Failure”

Delirium Breakdown

- 40-45% of cases missed by med/surg services
- Hypopactive delirium most often missed
  - Less agitation
  - Psychomotor slowing
  - Staring/catatonia
- Mixed type waxes/wanes
The System Impact

- Inpatient LOS 5-10 days longer
- Hospital costs increased by 1.3-2.5x
- $38-152 billion total cost annually
- Only 14% return to baseline cognition before d/c
- NHP necessary in 16% vs 3% general hospital population
- 6-month mortality after ICU 34% vs 15%
Why Does Delirium Happen?
The Original Model...

Physical Illness → Dopamine++ → Delirium (Agitation)

Classic approach:
- Treat agitation
- “Fix” physiologic cause(s)
- OFTEN WORKS!!

Problematic because it:
- Depends on agitation
- Only works after the fact (no prevention)

Why Does Delirium Happen?
An Updated View

A Better Model...

"Vulnerable Brain"

Physiology

ACh

DA

SHT

NE

Agitation

Delirium

Hypoactive

Environment
Environment

- **SLEEP!**
  - ICU patient: 1.5 hours sleep/night
  - Light patterns
  - Pharmacologic "help"
- **Light Disruption**
  - Melatonin
  - Not so much deprivation as disturbing rhythm
- **Noise**
  - Sleep disruption
  - Contribution to hallucinations
- **Cultural Factors/PTSD**

Vulnerable Brain

- "Aging brain"
  - Decreased sensory perception → heightened sensitivity to environmental stimuli
  - Dementia/Cognitive Impairment
    - 40% of hospitalized patients w/dementia develop delirium
    - 100% of patients with pre-existing dementia undergoing hip/knee surgery developed delirium
  - Decreased Ach-producing cell mass → more sensitive to changes in Ach stimulation and prone to depletion
- Susceptibility to anticholinergic medicines
  - Benadryl, TCAs, oxybutynin
  - DRY MOUTH = DELIRIUM RISK

Vulnerable Brain

- Dopamine Agonists
  - Parkinson disease meds
    - Levodopa/carbidopa (Sinemet, Parcopa)
  - RLS Meds
    - Dopa
    - Pramipexole (Mirapex), Ropinirole (Requip)
  - Hallucinations, restlessness
  - Attention to recent dose increases
  - Decreasing body mass may mean lower dose is needed
Adrenergic Stress: Norepinephrine
- Critical illness
- Infection
- Trauma
- Drug/alcohol intoxication or w/d (also GABA, glutamate)

Acetylcholine (ACh)
- DRUGS!
- Aging

5-HT (serotonin): Liver disease, drugs

Dehydration: Decreased clearance of drugs, by-products

Dopamine: Psychomotor agitation

Delirium Types
- "Classic" delirium
  - Physiologic stress due to illness
  - Hospital-environmental stress

Sundowning
- Environmental stress in vulnerable brain

Terminal delirium/restlessness
- Dying process is the physiologic stress
- Spiritual/mystical overlay

Long Term Cognitive Impact
- 225 patients age >60
- Postop from cardiac surgery (CABG, AVR)
- MMSE
  - Baseline
  - During hospital course
  - 1, 6, 12 months after d/c
- Patients with delirium took up to a year to return to baseline
- Duration of delirium predicts longer recovery time

Saczynski JS et al. NEJM 2012 367:1 30-39
Delirium Assessment

- Alphabet Soup
- CAM, CAM-ICU
- NEECHAM
- MDAS
- Varying levels of time intensiveness and depth of evaluation
- Biased to hyper-active state

**Delirium Interventions**

**Causes**

- Vulnerable Brain

**Physiology**

- ACh
- DA
- 5HT
- NE

**Symptoms/Effects**

**Usually need to address both sides to improve delirium**
Treating Delirium
The Argument for Environmental Intervention

Treating Delirium
The Argument for Environmental Intervention

Figure 1. Cumulative Incidence of Delirium According to Study Group.

PAIN MAKES EVERYTHING WORSE
(Don’t forget to address and treat pain)
Pharmacologic Intervention

- Behavioral means often not enough
  - Delirium recognized late
  - Hypoactive/hyperactive transition

- Key Questions:
  - Is delirium threatening patient or staff safety acutely?
  - Is the patient's medical condition worsening or plateauing because of delirium?
  - Refusing treatments
  - Not eating/drinking
  - Needing sitter→can't get to SNF

Pharmacologic Treatment

- Most of our data (and traditional approach) is about agitated delirium
  - Implies high dopamine state

- Two “classes” of drug
  - Typical antipsychotics
    - Haloperidol, chlorpromazine
    - Block D2 receptor (also ACh, H)
  - Atypical antipsychotics
    - Risperidone, olanzapine, quetiapine
    - Block D2, 5-HT

Treating Delirium

Do Antipsychotics Work?

- Trial of two approaches to treatment of agitated delirium in ICU
- “Usual Care” managed by ICU teams (Med, Surg)
  - No formulary restrictions, tended toward PRN antipsychotics/benzos
- “PMS” (Psychosomatic Medicine Service) team
  - Scheduled IV haloperidol QID, daily dose adjustment
  - Minimal benzo use
**Treating Delirium**

The Argument for Antipsychotics


![Graphs showing delirium outcomes with Haldol and Atypicals](image)

**Haldol vs. Atypicals**

- Cochrane Review 2007
  - Lonergan E, Cochrane Database Syst Rev. 2007 Apr 18(2):CD005594
- Haldol versus
  - Risperidone
  - Olanzapine/placebo
  - Placebo for prevention after hip surgery in high-risk patients
- All equally effective, similar AE profiles until haldol dose >3.5 mg/day (EPS)

**The 2018 Updates**

- 247 palliative care patients in Australia
- Usual care + randomization to
  - Haldol 0.5 mg BID
  - Risperidone 0.5 mg BID
  - Placebo
- Use of midazolam as "rescue"
  - Increased in H/R groups
- Increased mortality in H/R
My (Over)reaction

- But wait...
  - Dose and schedule of H/R do not match usual practice
  - Is increased mortality due to H/R or midazolam?
- We still give Haldol for delirium
  - But I think more about dose and schedule

The 2018 Updates

- 93 patients with delirium in context of advanced cancer
- Randomized to
  - IV Haldol (2mg q4h + 2q1h PRN) + placebo
  - IV Haldol + lorazepam 3 mg IV q4h
- Outcome: sedation level (RASS)
- Sedation better with lorazepam
- Delirium NOT WORSE

My Reaction

- Lorazepam is sedating... **duh**.
- Haldol was sedating too
- What should our goal be in treating terminal delirium?
  - Are we treating the disease process or ONLY reducing symptom burden?
- Informs my discussion of treatment goal
  - More often recommending sedation
Preventative Haldol?

- 1789 ICU admissions
- Excluded:
  - Neuro event
  - Delirious
  - Haldol 1 or 2 mg TID versus placebo
- Primary QC: Mortality at 28, 90d
- No statistical differences

How do We Decide?

- Haldol or an atypical?
- Cost, familiarity and setting
- What can/will the patient take?
  - Dose forms
  - Speed of onset
- Side Effects
  - QT prolongation
  - Sedation potential

How do We Decide?

- Haldol = “morphine of agitation”
  - Cheap
  - Readily available
  - Many dose forms (NOT transdermal)
- BUT...people are scared of haldol
  - “Black box” warning
  - NH/SNF setting = haldol is bad (but there are no good antipsychotics)
  - It doesn’t always work
Antipsychotic Daily Dose Equivalents

- Haloperidol 2 mg ~ Chlorpromazine 100 mg
  - Risperidone 2 mg
  - Olanzapine 5 mg
  - Quetiapine 75 mg
  - Ziprasidone 60 mg
  - Aripiprazole 7.5 mg

Adapted from Woods SW. J Clin Psychiatry 2003 Jun;64(6):633

Antipsychotics and QTc

<table>
<thead>
<tr>
<th>QTc Prolongation</th>
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<tbody>
<tr>
<td>Quetiapine</td>
<td>+14.5 ms</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+ 10.0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+ 6.4</td>
</tr>
<tr>
<td>Haldol (oral)</td>
<td>+ 4.7</td>
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</tbody>
</table>

IV haldol and thorazine more, ? how much

Haddad, PM and Anderson, IM. Drugs 2002; 62 (11): 1649-1671

When Do I Get an ECG?

- My anxiety is proportionate to total dose and goals of care
- Known baseline QTc elevation
- Recent cardiac procedure/event with no subsequent ECG
- Other QTc prolonging meds
  - Amiodarone
  - Sotalol
  - Methadone (esp doses >100 mg/day)
  - Diuretics (K/Mg reduction)
- Repeat x1 after 2 days, if no events not necessary to recheck unless long-term Rx (?)
### Antipsychotics and Sedation

**Medication** | **Sedation Potential**
---|---
Chlorpromazine | +++
Clozapine | +++
Olanzapine | ++
Quetiapine | ++
Haloperidol | +
Aripiprazole | +
Risperidone | +
Ziprasidone | +

Adapted from Muench J, Hamer AM. *Am Fam Physician* 2010 Mar 1;81(5):617-622

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### PRN Only??

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### Mild Delirium

- Would sedation be a good thing?
  - Informed consent discussion
- Less sedating:
  - Haldol 1 mg q6h and 1-2 mg q2h PRN
- More sedating:
  - Quetiapine 12.5-25 mg PO TID + PRN
- If sundowning, will give scheduled dose ~1600-1800
**Major Agitated Delirium**

- Haldol 1-2 mg IV or 2-5 mg SL, repeat q30 min until agitation decreases
  - Can also escalate dose if 1 mg not effective
  - Alternative: Chlorpromazine 25-50 mg
- Total up effective “loading dose,” divide TID over next 24h
  - Example: 3 doses of 1 mg haldol effective to calm patient → schedule 1 mg PO q8h
- Sedation usually is a good thing
- Patient may sleep for >24 hours if significantly sleep deprived

**Adjuvants: Depakote**

- Case Series, n=6, unblinded
- Addition of low-mod dose valproate to antipsychotics or benzos
  - Variety of clinical causes
  - Often after AE from antipsychotic or benzo
- Success reported in all cases

**Adjuvants: Depakote?**

- Systemic review, meta-analysis of 3 RCTs
- Valproate for agitation in dementia patients
- No effectiveness found
- Arguably, dementia and delirium are different processes, but it casts doubt
- I have used when antipsychotics not effective alone but with caveats
**Adjuvants: Methylphenidate**

- No randomized data
- Theoretically should be good for hypoactive state
- 14 advanced cancer patients
- Hypoactive delirium
- Average 6-point gain in MMSE with treatment (statistically significant)

**Caregivers...**

- Often experience worst of symptoms
- Are called on by staff to help manage patients at their worst moments
- Are fearful that their loved one is developing dementia
- Often have no prior knowledge that delirium is a problem

**Treating Family and Caregivers**

- Address fears of developing dementia
  - Stress acute and reversible nature of delirium
  - Normalize waxing/waning status
  - Emphasize use of meds for comfort and calming, helping to sleep
- Sleep:
  - If patient has relatively mild sleep/wake disturbance, can try to keep awake during day
  - If severe agitation, let sleep
  - May be 1-2 days of “lost time”
Treating Family and Caregivers

- Recovery phase is often most difficult one behaviorally
  - Frustration
  - Continued hallucinations with some insight
- Temptation to stop pharmacologic interventions too soon
- They have the most impact on environment interventions in home setting

Treating Family and Caregivers

- Analogy of snow globe
- Delirium is “storm,” many factors shaking the globe
- Key is to try to keep things calm until snow settles

Key points

- Delirium is a common and complex syndrome with serious impacts including profound suffering
- Awareness of the diagnosis and addressing risk factors are crucial
- Treatment involves pharmacologic, behavioral and caregiver factors