American Academy of
Hospice and Palliative Medicine

DELIRIUM

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AAHPM Intensive Board Review Course

Delirium

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Disclosure Information

Michelle Weckmann, MS MD
Has no relevant financial relationships to disclose.

Objectives

- Review prevalence, diagnosis and treatment of delirium at the end of life
- Brief review of agitation at the end of life

Delirium

- Also called: acute confusional state, encephalopathy, organic brain syndrome, terminal restlessness, terminal agitation or intensive care unit psychosis
- Very common
  - 25-40% in cancer patients
  - up to 85% in the terminal stages
- Often mistaken for depression or anxiety
  - Emotional alterations are common associated features

DSM-IV TR

A. **Disturbance of consciousness** with reduced ability to focus, sustain or shift attention
B. A **change in cognition** or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia
C. The disturbance **develops over a short period of time** (usually hours to days) and tends to **fluctuate** over the course of the day
D. There is evidence from the history, physical exam, or laboratory findings that the disturbance is **caused by** the direct physiological consequences of **a general medical condition**

Delirium Prevalence

- Up to 90% in hospice inpatients with cancer
  - Median survival from delirium onset to death is 10 days
  - Etiology
    - 42% dehydration
    - 29% liver failure
    - 25% medication
- 50% home hospice patients reported as confused in previous week by RN

Morita, J Pain Symptom Manage 2001
Nowels, J Pall Med 2002

Delirium and Depression

- Often co-morbid and symptoms commonly overlap
- 100 pts admitted to inpatient hospice (Leonard 2009)
  - 34% diagnosed with delirium
  - 30% diagnosed with subsyndromal delirium
  - 37% diagnosed with major depressive disorder (MDD)

54% patients with delirium had core features of MDD (38% of subsyndromal)

- Is the depression real or just a delirium sub-type?
- Need to rule out delirium before we diagnose depression

Delirium and Dementia

- Age and cognitive impairment are the strongest risk factors for developing delirium
- Can be difficult to separate out
- Delirium may be a precursor to a dementia and may cause long lasting cognitive changes

Differential Diagnosis of Dementia, Depression and Delirium

Clinical Feature	Dementia	Depression	Delirium
Onset	Insidious (months to years)	Acute or insidious (weeks to months)	Acute (hours to days)
Duration	Months to years	Months to years	Hours to weeks
Course	Chronic and progressive	May be chronic	Fluctuating
Progression	Irreversible	Usually reversible	Usually reversible
Level of Consciousness	Usually clear	Clear	Altered
Orientation	Disoriented	Oriented	Variable
Attention	Intact except in late stage	May be decreased	Impaired
Concentration	Intact except in late stage	May be decreased	Impaired
Speech	Coherent until late stage	Coherent (may be latent in severe)	May be incoherent or latent
Thought Process	Limited	Organized	Disorganized
Perception	May have hallucinations (paranoia more common)	Mood congruent hallucinations in severe cases	Hallucinations are common (often visual)
Psychomotor activity	Variable	May be slowed in severe cases	Variable
Sleep pattern	Variable	Often increased but may have early AM awakenings	Variable, days and nights commonly confused

From What Is Delirium? (Table 2), by M Weckmann, in N Goldstein, S Morrison (Eds.), Evidence Based Practice of Palliative Medicine, 2011, Elsevier. ©2011 Elsevier. Reprinted with permission.

Why Identify? Why Treat?

- Common
- Shortens life expectancy
  - 6 month mortality up to 25%
- 50% of hospitalized patients with delirium are discharged before delirium resolves
  - 20% patients discharged home placed within 1 year
- Increases chance of nursing home placement from hospitalization (73% vs 30%)
- Distressing to patient and family
- Robs patients of time and decreases opportunities to make final plans and decisions
- Increases hospital LOS and cost

Risk Factors for delirium

- Vision impairment
- Medical illness
- Cognitive impairment
- Age >70
- Any iatrogenic event
- Physical restraints
- Malnutrition
- Add >3 meds
- Hypertension
- COPD
- ETOH abuse
- h/o smoking
- Abnl labs
- Foley
- Functional limitations
- Prior delirium
- Medications (benzos, opioids, anticholinergic)
- Epidural
- Constipation

Medications that can cause delirium

- Anti-cholinergics (i.e., diphenhydramine, atropine, scopolamine)
- TCA's
- Anti-inflammatories (i.e., NSAIDS, steroids)
- Benzodiazepines (i.e., valium, zolpidem)
- Cardiovascular (i.e., digoxin, antihypertensives)
- Diuretics (furosemide)
- GI (ranitidine)
- Lithium
- Opioids

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Why consider screening for delirium?

- Majority of delirium is missed or not diagnosed
- Delirium has short and long term impact for everyone involved (pt, family, healthcare providers)
- Delirium can be reversed in over 50% of the cases
- Treatment of delirium improves long term outcomes

Delirium Screening Instruments

- Multiple instruments
- Good review articles
- CAM-ICU great for ICU patients
  - Not effective out of the ICU
- CAM- sensitivity/specificity depends on training
- All screening tests require some sort of cognitive testing
- Delirium is a clinical, bedside diagnosis

Screening recommendations

- SQiD (single question in delirium)
  - *"Do you think [insert pt name] has been more confused lately?"*
  - 80% sensitive and 71% specific in inpt oncology patient
- Basic cognitive tests
  - Verbal trails (alternate alphabet and numbers to 10)
  - Days of week or months of year backwards
  - Clock-draw
  - Count backwards from 20 to 1 (good for dementia pts)

Delirium management

1. Make diagnosis
2. Support/educate patient and family
3. Non-pharmacologic interventions
4. Establish goals (need prognosis)
5. Consider work-up/treatment of potentially correctible etiologies
6. Aggressively treat distressing symptoms

50% of delirium can be reversed even when patients are in the final days of life

Delirium Type

- 25% hypoactive
- 25% hyperactive
- 50% mixed

Delirium Basic Evaluation

1. Good history and physical
   - Pain assessment - constipation
   - Medication review - dehydration
2. Tests (if indicated/desired)

Initial investigation	More specific tests	Reasons to order specific tests
Complete blood count	Electrocardiogram	Existing cardiac disease
Blood urea and nitrogen levels	C reactive protein (CRP) and erythrocyte sedimentation rate (ESR)	Suspected inflammatory disease
Electrolytes	Urinalysis, urine and blood cultures, Chest X-ray	Suspected infection
Blood sugar	Urine toxicology screen	Suspected drug use
Liver function	Vitamin B12, folate	Malnutrition
Thyroid function	EEG	Suspected seizures
Arterial blood gases	Computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the brain	Suspected cerebral cause (stroke or brain metastasis)
	Lumbar Puncture (LP)	Suspected meningitis

From What Is Delirium? (Table 5), by M Weckmann, in N Goldstein, S Morrison (Eds.), Evidence Based Practice of Palliative Medicine, in press, Elsevier. ©2011 Elsevier. Reprinted with permission.

Non-pharmacologic Interventions

- Cognitive
  - Orientation (calendar, caregiver names)
  - Activities (cognitively stimulating)
- Sleep
  - Regular routine
  - Sleep aids (relaxing music, massage)
  - Environmental (eliminate noise, night-time meds)
- Mobility (range of motion, limit IV's, etc)
- Visual Aids (glasses, large dial phones, etc)
- Hearing Aids (check ear wax)
- Volume repletion for dehydration (beverage of choice available and offered frequently)

Other Delirium Interventions

- Opioid rotate esp if Opioid Induced Neurotoxicity is suspected
  - (methadone and fentanyl preferred)
- PCA for pain control
- Methylphenidate has been used for hypoactive delirium
- Rehydration (oral, hypodermoclysis or IVF)
- Music reduced post-op delirium in elderly

Pharmacologic Treatment

- No medication is FDA approved for the treatment of delirium
- No published double-blind, randomized, placebo controlled trials
  - Few controlled trials
  - Small numbers
  - Various patient populations
    - post-op, ICU, cancer, AIDS, hip fractures

Haldol v. Lorazepam

- Double-blind RCT
- 244 AIDS patients consented
- 30 (12%) patients developed delirium
- Haloperidol (n =11)
- Chlorpromazine (n = 13)
- Lorazepam (n = 6)
- Haloperidol = chlorpromazine > lorazepam

Delirium Treatment

- No FDA approved medication for delirium
- Anti-psychotics are the treatment of choice
  - Have been shown to both prevent as well as resolve delirium
- All antipsychotics have suspected efficacy
- Typicals (haloperidol, chlorpromazine) have greatest evidence base, are cheaper, and have multiple routes of administration

Antipsychotics and Mortality

In Dementia

- Black Box Warning Issued in 2004
- Consistent across all antipsychotics
- Relative risk = 1.6-1.7
  - Absolute risk = 3.5% vs. 2.3% with placebo
- Number Needed to Harm = 83
  - Number need to treat = 5-14
  - For every 9-25 persons helped, 1 death associated with use

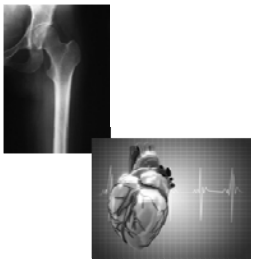
In Delirium

- No evidence that mortality is increased

Elie, 2009
Jeste, 2008

Antipsychotic Adverse Effects

- Sedation
- Postural hypotension
- Falls
- Extrapyramidal
  - Parkinsonism
- Cerebrovascular
  - OR 2.1, ARI ~1%
- Mortality
  - Infection and cardiac
- Metabolic side effects (weight gain, etc.)



Antipsychotic Side Effects

Drug (daily dose range) *Brand Name*	Aripiprazole (2-10 mg) *Abilify*	Haloperidol (0.25-2 mg) *Haldol*	Olanzapine (2.5-7.5 mg) *Zyprexa*	Quetiapine (12.5-150 mg) *Seroquel*	Risperidone (0.25-2 mg) *Risperdal*
Movement Side Effects[1]	■■	■■■	■■	■	■■
Central Nervous System					
Sedation	■■	■■	■■■	■■■■	■■
Confusion, delirium, other cognitive worsening	■	0	■■	■	■
Worsening psychotic symptoms	0	0	■	0	0
Cardiovascular /Metabolic					
Orthostatic hypotension	■?	■■	■	■?	■?
Edema	■?	0	■	0	■■
Weight gain/glucose ↑	0	■?	■■■	■	■■
Triglyceride ↑	0	0	■■■■	■■■	0
Urinary incontinence/UTI	■■■	■■	■■	■■	■■

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Common Antipsychotics

Typical	Atypical
• Chlorpromazine (Thorazine)	• Risperidone (Risperdal)
• Thioridazine (Mellaril)	• Ziprasidone (Geodon)
• Prochlorperazine (Compazine)	• Olanzapine (Zyprexa)
• Haloperidol (Haldol)	• Quetiapine (Seroquel)
• Fluphenazine (Prolixin)	• Clozapine (Clozaril)
• Perphenazine (Trilafon)	• Aripiprazole (Abilify)

What about 2nd Generation Antipsychotics ?

Haloperidol is EQUAL to:

- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Aripiprazole (Abilify)

Han , 2004
Skrobik, 2004

Typical Formulations

Generic names	Relative Potency	Available Formulations	Considerations
Chlorpromazine (Thorazine)	100	tabs, liquid, IM/SQ, suppository	May be more effective for highly agitated patient. More anticholinergic. Can help with hiccups.
Thioridazine (Mellaril)	95	tabs, liquid	More cardiac concerns.
Haloperidol (Haldol)	2	tabs, liquid, IM/SQ	Can help with nausea. Gold standard for delirium.
Fluphenazine (Prolixin)	2	tabs, liquid, Long acting IM/SQ	Vey similar to haloperidol
Perphenazine (Trilafon)	8	Tabs, liquid, IM	Often not recognized by family/care centers

Atypical Formulations

Generic names	Relative Potency	Available Formulations	Considerations
Risperidone (Risperdal)	3	Tab, liquid, rapid dissolving (SL)	Very similar to haloperidol
Ziprasidone (Geodon)	60	Caps, **IM**	Little data for delirium
Olanzapine (Zyprexa)	5	Tab, **IM**, rapid dissolving (SL)	More sedating, can worsen delirium
Quetiapine (Seroquel)	100	Tabs	1st line in Parkinson's
Clozapine (Clozaril)	100	Tabs	Needs intensive monitoring, 2nd line in Parkinson's
Aripiprazole (Abilify)	7.5	Tab, liquid, **IM**, disk melt (SL)	Little data for delirium

Common Medication Doses

Antipsychotics

- Haloperidol 0.5-1mg Q30min
  - PO has ½ life of 24 hr
  - IV has ½ life of 12 hrs
- Chlorpromazine 25-50 mg PO/PR TID-QID
- Olanzapine 2-5 mg PO/SL QD
- Risperidone 0.5 mg PO/SL BID
- Quetiapine 50-100 mg PO BID

Sedatives

- Lorazepam 0.5-1mg PO/IV/SQ q4hr
- Diprivan (Propofol) 10mg IV bolus (then 10mg/hr)
- Midazolam 1-2mg IV q1hr

Terminal Delirium

- Is it just part of normal dying?
  - Accumulation of toxic metabolites
  - Electrolyte disturbances
  - Organ failure
- Diagnosis usually made retrospectively
  - Significant restlessness/agitation in final days of life
- Common reason for palliative sedation

Terminal Delirium

- Treatment recommendations (IV or SQ)
  - Antipsychotic (higher doses)
  - If antipsychotic is ineffective consider high dose benzodiazepines
  - If sedation is desired consider a sedative agent (phenobarbital, propofol)
- Case Study
  - 83 year old, end stage lung cancer, previously independent, in care center for failing ADLs
  - Restless, agitated, pacing, striking out
  - Started SQ Chlorpromazine 20mg/hr with 20mg q30min bolus-increased to 100mg/hr with 50mg q30min bolus
  - Was comfortable, confused, conversant, not pacing or striking out in last 2 days before death

Delirium Pearls

- Very common and distressing- maintain a high index of suspicion
- Can often be reversed by simple measures even in dying patients
- Treat symptoms aggressively to improve long-term outcome
- Anti-psychotics (haloperidol/chlorpromazine) are treatments of choice for distressing symptoms

Behavioral Disturbances

- Common in **dementia** and **delirium**
- Disruptive physical behaviors
  - Wandering, pacing
  - Physical threats or violence
- Disruptive verbal behaviors
  - Verbal outbursts/aggressiveness
  - Disruptive vocalizations

What to do: Behavioral Disturbances

- Try to remove things that aggravate
- Consider pain, medical conditions, hunger, thirst
  - Food refusal, resisting cares such as bathing
- Remember not to TEACH
- Try to distract to something else

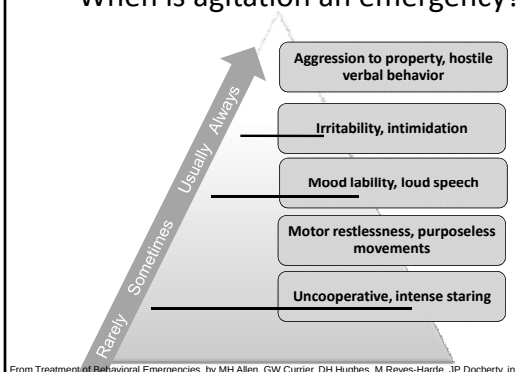
What to do for psychosis?

- Don't argue or "point out the truth"
  - Reassure, distract to something pleasant
    - E.g., don't repeatedly remind of spouse/parent's death, etc
- Identify the symptoms
  - Visual? Tactile? Delusions? Misperceptions?
- Consider medications (i.e., Sinemet) or illness which may be contributing

What to do in general?

- Deal with fluctuations
  - Don't blame
    - What works one day doesn't always work the next
- Expectations
  - Symptom reduction or stabilization may = success
  - Focus on quality of life, daily function, autonomy

When is agitation an emergency?



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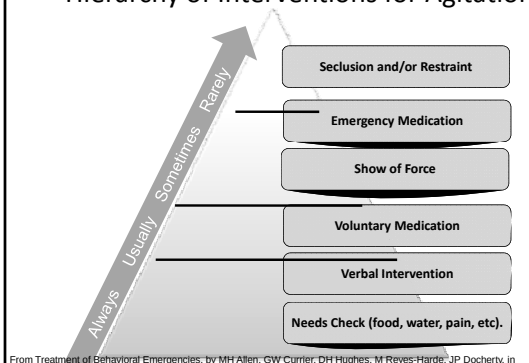
Hierarchy of Interventions for Agitation



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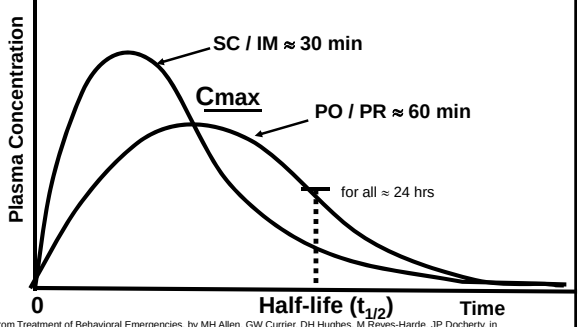
Drug treatment for Agitation

- Antipsychotics most commonly used
- Treat agitation like another breakthrough symptom
- Start with prn dosing and dose on the Cmax
- Calculate scheduled dose based on needed prn amount in previous 24 hrs

Antipsychotic Pharmacokinetics



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Moderate Agitation

- Haloperidol 1-2 mg SQ/PO
  - Increase dose by 1 mg q Cmax until controlled
- Alternatives
  - Chlorpromazine 50-100 mg SQ up to 2g/d
    - Increase dose by 50 mg q Cmax until controlled
    - SQ can burn, infusing 1 mg dexamethasone q24hr can help
    - Oral bio-availability variable, more sedating
  - Risperidone 0.25-1mg PO q1hr up to 6 mg/d
  - Olanzapine 5-10 mg PO q1hr up to 30 mg/d
  - Quetiapine 25-100 mg PO q1hr up to 1200 mg/d

Severe Agitation

- Imminent risk of harm to self or others due to agitation
  - Haloperidol 2-5 mg x 1
  - ± diphenhydramine* 50-100 mg
    - Protects against EPS and adds sedation
  - ± lorazepam* 1-2 mg
    - Can also consider midazolam

* Mix very slowly in order in same syringe:
- Lorazepam ▶ Haloperidol ▶ Diphenhydramine

Severe Agitation

- Alternatives
  - Chlorpromazine 50-100 mg SQ up to 2g/d
    - Increase dose by 50 mg q Cmax until controlled
    - Likely don't need diphenhydramine
    - Use ± lorazepam
  - Olanzapine 5-10 mg IM up to 30 mg/d
    - MR x 1 in 2hrs, MR x 1 again 4 hours after that
    - Expensive
  - Ziprasidone 10-20 mg IM up to 40 mg/d
    - MR 10 mg q2 hrs
    - MR 20 mg q4 hrs
    - Expensive

Dementia Related Agitation

- Antipsychotics may no longer be first line
- Consider behavioral/non-pharm techniques first
- Some evidence for:
  - Beta-blockers
    - Propranolol 10 mg qd to 160 mg tid (start 20-40 mg bid)
  - Gabapentin
    - 100 – 300 mg q1hr up to 3600 mg/d
  - Trazodone
    - 25 – 50 mg q1hr up to 300 mg/d
  - Acetylcholinesterase inhibitors
  - High dose SSRIs

Agitation Pearls

- Treat agitation like you treat pain
- Dose break-through on Cmax
- Dose scheduled on ½ life
- Use time limited trials

- References for agitation management in dementia and delirium (pocket cards, video vignette training and more)

http://www.healthcare.uiowa.edu/igec/IAADAPT/

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Death is a very dull, dreary affair, and my advice to you is to have nothing whatsoever to do with it.
--W. Somerset Maugham

Differential Diagnosis of Dementia, Depression and Delirium

Clinical Feature	Dementia	Depression	Delirium
Onset	Insidious (months to years)	Acute or insidious (weeks to months)	Acute (hours to days)
Duration	Months to years	Months to years	Hours to weeks
Course	Chronic and progressive	May be chronic	Fluctuating
Progression	Irreversible	Usually reversible	Usually reversible
Level of Consciousness	Usually clear	Clear	Altered
Orientation	Disoriented	Oriented	Variable
Attention	Intact except in late stage	May be decreased	Impaired
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Speech	Coherent until late stage	Coherent (may be latent in severe)	May be incoherent or latent
Thought Process	Limited	Organized	Disorganized
Perception	May have hallucinations (paranoia more common)	Mood congruent hallucinations in severe cases	Hallucinations are common (often visual)
Psychomotor activity	Variable	May be slowed in severe cases	Variable
Sleep pattern	Variable	Often increased but may have early AM awakenings	Variable, days and nights commonly confused

Delirium Basic Evaluation

1. Good history and Physical
   - Pain assessment - constipation
   - Medication review - dehydration
2. Tests (if indicated/desired)

Initial investigation	More specific tests	Reasons to order specific tests
Complete blood count	Electrocardiogram	Existing cardiac disease
Blood urea and nitrogen levels	C reactive protein (CRP) and erythrocyte sedimentation rate (ESR)	Suspected inflammatory disease
Electrolytes	Urinalysis, urine and blood cultures, Chest X-ray	Suspected infection
Blood sugar	Urine toxicology screen	Suspected drug use
Liver function	Vitamin B12, folate	Malnutrition
Thyroid function	EEG	Suspected seizures
Arterial blood gases	Computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the brain	Suspected cerebral cause (stroke or brain metastasis)
	Lumbar Puncture (LP)	Suspected meningitis

Antipsychotic Side Effects

Drug **(daily dose range)** ***Brand Name***	**Aripiprazole** **(2-10 mg)** ***Abilify***	**Haloperidol** **(0.25-2 mg)** ***Haldol***	**Olanzapine** **(2.5-7.5 mg)** ***Zyprexa***	**Quetiapine (12.5-150 mg)** ***Seroquel***	**Risperidone** **(0.25-2 mg)** ***Risperdal***
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Central Nervous System					
Sedation	■■	■■	■■■	■■■■	■■
Confusion, delirium, other cognitive worsening	■	**0**	■■	■	■
Worsening psychotic symptoms	**0**	**0**	■	**0**	**0**
Cardiovascular /Metabolic					
Orthostatic hypotension	■**?**	■■	■	■**?**	■**?**
Edema	■**?**	**0**	■	**0**	■■
Weight gain/glucose ↑	**0**	■**?**	■■■	■	■■
Triglyceride ↑	**0**	**0**	■■■■	■■■	**0**
Urinary incontinence/UTI	■■■	■■	■■	■■	■■

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Typical Formulations

Generic names	Relative Potency	Available Formulations	Considerations
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Aripiprazole (Abilify)	7.5	Tab, liquid, **IM**, disk melt (SL)	Little data for delirium

Delirium

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