Delirium In the Hospitalized Patient

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Disclosures

- No Financial Disclosures
- We WILL be discussing "OFF LABEL" use of medications
  - Any antipsychotic used in the treatment or prevention of delirium is "OFF LABEL"

Goals

- Define delirium
  - Understand the differences between Dementia and Delirium
- Understand the importance of delirium as it pertains to morbidity and mortality
- **Be able to identify delirium using standardized assessment scales (clinical assessment)**
- **Recognize potential causes of delirium**
- Understand possible preventative strategies
- Improved understanding of the **treatment** (pharmacological and nonpharmacological) of delirium in the hospital setting
  - And limitations of data

Goals

- Will not be discussing management of delirium due to Drug Withdrawal (ETOH, Opiates, etc.)
  - These syndromes remain important in your differential diagnosis.
- Will NOT discuss the ICU(vented) patient
- Intended as a discussion for the general medical/surgical patient

Definition

- **An acute state of confusion marked by**
  - **Sudden Onset**
  - **Fluctuating Course**
  - **Inattention**
  - **At times, abnormal level of consciousness**
- **Symptoms can also include**
  - **Sleep disturbances**
  - **Agitated behaviors**
  - **Delusions and Visual Hallucinations**
- Identifiable cause (s)
- Other terms used include *organic brain syndrome, metabolic encephelopathy, toxic psychosis, acute mental status change, exogenous psychosis, sundowning*

Definition

- Disturbance of Consciousness
  - Reduced clarity of awareness of the environment
  - **Reduced ability to focus, sustain, or shift Attention**
- A **Change in Cognition**
  - Memory, Disorientation, Language OR
- Development of a perceptual disturbance not better accounted for by a pre-existing, established, or evolving dementia (notes)
- Develops over a **short period of time (usually hours to days**) and **tends to fluctuate** during the course of the day
- There is evidence from the history, PE, or Lab that the disturbance is caused by the direct physiological consequences of a general medical conditions

Delirium Subtypes

Hyperactive (three or more) (30%)
- Hypervigilance
- Restlessness
- Fast/loud speech
- Anger/irritability
- Combativeness
- Impatience
- Uncooperative
- Laughing
- Swearing/singing
- Euphoria
- Wandering
- Easy startling
- Distractibility
- Nightmares
- Persistent thoughts

Hypoactive (four or more) (24%)
- Unawareness
- Lethargy
- Decreased Alertness
- Staring
- Sparse/slow speech
- Apathy
- Decreased Motor Activity

Mixed (46%)
Characteristic waxing and waning
Agitated/Combative ← →
Somnolence/Hypoactive

Data from Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992;161:843–5.

Epidemiology

- ***At admission*** prevalence 14-24%
- Hospitalization incidence 6 to 56%
- 15-53% geriatric patients post-op
- 65% of patients with baseline dementia will experience delirium in the hospital
- **70-80% older patients in ICU**
- 60% nursing home will have at some time
- 83% of geriatric patients prior to death

Epidemiology -- MaineGeneral

- Chart Review from January 2016
- 157 patients, 70 or older admitted to 1W, 2W or 3W
  - Prevalence of delirium on admission, 23%
  - Incidence of delirium during hospitalization, 12%
  - 35% of patients 70 or older will have delirium during hospitalization

Delirium Outcomes

- **Mortality** rate in hospitalized patients **22-76%**
- One year mortality rate is **35-40%**
- **Prolongs hospital course/Increased cost of care** in hospital
  - $16,000 to $64,000 more per patient w/ delirium
  - Burden est. at $38 to $152 BILLION/year in U.S.
- Increases **likelihood of disposition to nursing home, functional decline** and loss of independence
- Strong association with underlying dementia – **3.5 x as likely to develop dementia in a 5 years**
- Frequently, **patient may never return to baseline or take months to over a year to do so**
- Delirium is often the sole manifestation of serious underlying disease
- **MGMC – LOS without delirium 5.4 days, with delirium 11.7 days**

Pathophysiology

- EEG shows diffuse cortical slowing
  - Does not correlate with underlying causes
- Neuropathology and imaging
  - Disruption of higher cortical function
    - Prefrontal cortex
    - Subcortical structures
    - **Thalamus**
    - Basal ganglia
    - Frontal and temporoparietal cortex fusiform cortex
    - Lingual gyri
    - Effect greatest on non-dominant side.

Pathophysiology

Nonspecific manifestation of a widespread reduction in cerebral metabolism & derangement of neurotransmission due to:
- Cholinergic deficiency
- GABA
- Dopamine
- NE
- Specific receptors (e.g., steroid)
- Alteration of blood flow, inflammation
- MULTIFACTORIAL

How can you tell who will develop delirium (what are the risk factors)?

Audience Participation

Delirium Risk Factors

Predisposing
- Age
- Cognitive impairment
  - 25% delirious are demented
  - 40% demented in hospital delirious
- Male gender
- High number of meds
- Malnutrition
- Sensory impairment
- Depression

Precipitating
- Severe illness
- Hip fracture
- Surgery/Anesthesia
- New Psychoactive medications
- Lines/catheters/restraints
- Metabolic disorders:
  - Azotemia
  - Hypo- or hyperglycemia
  - Hypo- or hypernatremia
- Alcoholism/Withdrawal
- Pain
- ***Sleep Deprivation***
- Infection (UTI, etc)

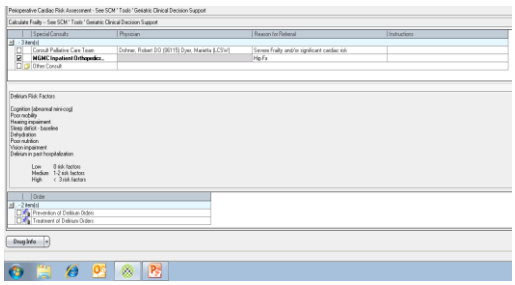
Risk Factors

- Risk is cumulative
  - Predisposing factors + Precipitating factors
- Defining risk
  - Predictive Model
    - 4 characteristics: Vision Impairment, Severe Illness Cognitive Impairment (Hx, MMSE >24), BUN/CR Ratio >18
    - 1 point for each: 0 = Low
    - 1-2 = Intermediate
    - 3-4 = high risk

Risk Factors

- In order of statistical relevance
  - Predisposing: Comorbid Conditions (>3), Cognitive Impairment, Age over 80, Age over 65
  - Precipitating: Polypharmacy (>3 new drugs), Fracture on Admission, Illness Severity (APACHE > 16), Infection
- Risk of prolonged Delirium
  - Cognitive Impairment (at baseline), Restraints, Sensory Deprivation (Vision)

Delirium Risk Factors



Causes

D **Drugs, Drugs** and toxins, too
E Eyes, ears – sensory deprivation
L Low O2 states (MI, ARDS, PE, CHF, COPD, stroke, shock)
I Infection
R **Retention** (of urine or stool). Restraints
I Ictal (post) = seizures
U Underhydration, Undernutrition
M Metabolic (hypo/hyper glycemia, calcemia, uremia, liver failure, thyroid disorders)
S Sleep Deprivation, Sedation(over), Stroke
Always add **P for Pain**

Drugs

- Accounts for 30% of all cases
- Common culprits
  - Anti-histamines
  - Anti-cholinergics
  - Antibiotics (Fluoroquinolones)
  - Some antidepressants
  - Dopamine agonists
  - **Hypoglycemics**
  - Benzos
  - Opiates
  - Cardiovascular – Amiodarone, Digoxin

Drugs

- History
  - Any new medication/new dose in the last several weeks; **medications recently discontinued (see case)**
- Syndromes
  - Hyperactive/Mixed Delirium – Cholinergic toxicity, Serotonin Syndrome, Stimulant Toxicity, ETOH/Benzo withdrawal
  - Hypoactive – Benzodiazepines, narcotic overdose, sedative/hypnotic/etoh intoxication

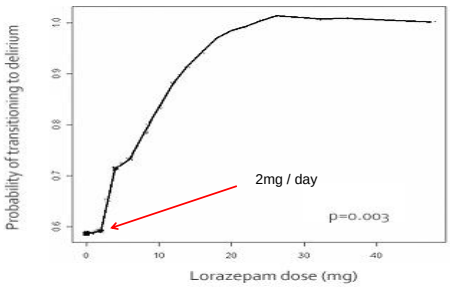
Case - 1

- 80 y/o female patient with hx of
  - mild cognitive impairment,
  - multiple medical comorbidities (CAD, CHF, Sleep apnea, obesity, refractory anemia, depression, Chronic UTIs on suppression
  - long term antidepressant (celexa)
  - started on Zyvox for a presumed UTI with VRE, subsequently fever delirium worsened over several days, with peak temp up to 103.6

Case -2

- 56 year old with hx of paraplegia from SC injury, admitted for cholecystitis
- Home medications included high dose fentanyl patch, Baclofen PO 20 mg TID → increased to 60 mg TID on admission
- Baclofen stopped abruptly after surgery – severe agitation, diaphoresis, confusion
- Baclofen withdrawal

Benzodiazepines

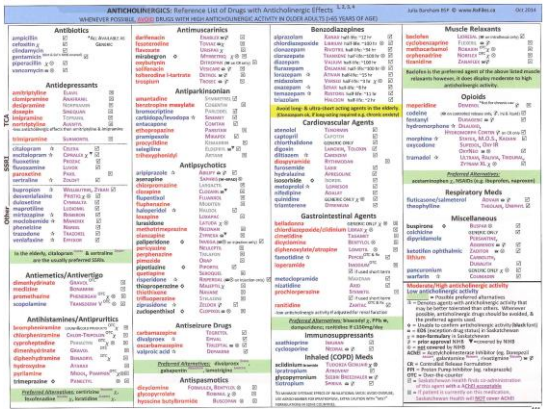


Opiates

- IV formulations more likely to cause delirium
- No difference between morphine or hydromorphone
- Post operative PCA did not increase delirium
- Methods to decrease amount of opiates may reduce delirium
  - Iliofascial nerve blocks for hip fracture patients
- ***Under-treatment*** of pain can lead to delirium

Anticholinergic Meds

High Anticholinergic Properties	Possible Alternatives
Antidepressants -- TCA – Tertiary amines (Amitriptyline), Doxepin	SSRI, TCA (nortriptyline)
Antihistamine (benadryl)	Second Generation (Loratadine)
Antiparkinson (Benztropine, Trihexiphenadyl)	Levadopa
H2 Blockers -- Cimetidine, Ranitidine	PPI
Antispasmodic – Oxybutynin	Tolterodine (Detrol)
Low Potency Antipsychotic (Chlorpromazine, Thioridazine)	Haldol (less anticholinergic than Atypicals)



A patient presents with acute agitation, or somnolence, you rightly consider delirium, what else is in your differential diagnosis?

Differential Diagnosis

- CNS pathology—stroke, infection, hemorrhage
- Dementia, particularly Lewy Body
- Other Psychiatric disorders
  - Psychosis
- Depression: **41% of hypoactive delirium misdiagnosed as depression** Farrell Arch Intern Med 1995
  - Bipolar disorder
- Aconvulsive status epilepticus
- Akathisia (restlessness from PD, w/drawal)
- *Overall, 32-67% missed or misdiagnosed*

Recognition: Finding Delirium

- We know it's there, we just need to look for it!

Confusion Assessment Method -- CAM

1. Acute change & fluctuation in mental status and behavior

AND

2. Inattention

AND EITHER

3. Disorganized thinking

OR

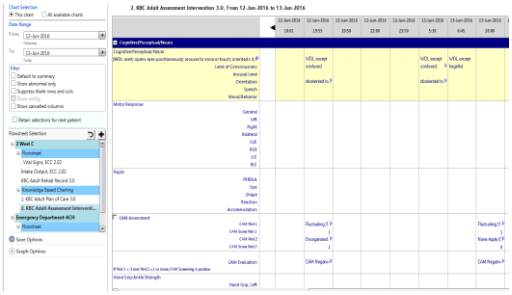
4. Altered consciousness (Hyper or Hypo)

Inouye SK et al. Ann Intern Med 1990;113:941-948.

CAM

- Sensitivity 94%, Specificity 89%
  - Endorsed in over 30 guidelines
- Limitations
  - Need training on how to administer
  - Should not be used alone, improved with specific **tests of attention**
  - Better accuracy when formal mental status testing done before using CAM (MMSE)
  - More on CAM-ICU later

CAM in SCM



Tests of Attention

- Digit span -- 5 numbers forwards, 4 backwards
- Days of week, **Months of year backwards**
- Go-no-Go test
  - ASLAP (squeeze), clapping hands
- Picture recall (CAM-ICU) if non-verbal
- Serial 7's or 3's
- Spell World Backwards

Assessment: Demonstration

- What I do
  - Mental status first – Alert, Hypervigilant, Lethargic, Stuporous, Coma
  - Orientation/recall of recent events/brief MMSE – clue to disorganized thinking
  - Attention (part of MMSE) and observation (distractible??)
  - History from outside sources

Recognition -- Summary

- Screen for Delirium on Admission (*Prevalence 27% at MGMC*)
- Screening includes:
  - History from outside sources (past hx of confusion = higher risk, recent change from baseline)
  - Review of risk factors (predisposing + precipitating)
  - Detailed Medication Review
  - Use CAM to screen/Dx but only in conjunction with other tests
    - Tests of attention

Delirium Workup

- **History**
  - Time course of change/baseline
    - Normal and recent *sleep* patterns
  - Recent events – fall, hospitalizations, **medication changes**, emotional stress, change in environment
  - **Medical History** –
    - Cognitive Deficits (ADLs/IADLs), **Past Delirium**
    - Comorbid conditions – risks for acute condition
      - COPD, CAD, hx of infections (UTIs), past Stroke
  - Sensory Deprivation – Vision, Hearing

Physical Exam and Diagnostics

- Vital signs/O2 Sat
- General exam
  - Pulm – look for tachypnea
  - Mental Status
  - Neuro findings
- Diagnostics
  - Labs: CBC, lytes, BUN, Cr, glucose, calcium, LFTs, UA, EKG (consider even for baseline), CXR
  - Drug levels (Digoxin, Theophylline, Anticonvulsants)

Diagnostics – cont'd

If routine labs are not revealing, consider:

- Neuroimaging -- not recommended routinely unless focal neuro exam, recent fall/trauma
- CSF – if indicated
- Tox screen/BAL, thyroid, B12, drug levels, ammonia, cultures, ABG
- EEG - in difficult cases to **r/o occult seizures** or psych disorders - **17% false neg, 22% false pos** – usually unrevealing in delirium

Workup

- Remember, Delirium is MULTIFACTORIAL
  - Even if one potential cause is found (UTI), consider contributing factors
    - Pain
    - Sleep
    - Dehyrdration/Undernutrition
    - Hypoxemia
    - Baseline cognitive impairment
    - Good chance to review and eliminate potential contributing long-term medications
      - Tylenol PM

Delirium Prevention

- Identify those at highest risk
- Environmental
- Pharmacological
- **Family Education**

Can Interventions Prevent Delirium?

- Inouye, et. al., 1999
- 852 **general medical** patients aged 70+
- Prospective matching of patients on intervention unit with patients on 2 usual care units
- Risk factor reduction strategy targeting:
  - Cognitive impairment
  - Sleep deprivation
  - Immobility
  - Visual impairment
  - Hearing impairment
  - Dehydration

>>HOSPITAL ELDER LIFE PROGRAM (H.E.L.P.)—**MGMC**

Intervention Protocol

• Cognition	Orientation, activities
• Sleep	Bedtime drink, massage, music, noise reduction
• Immobility	Ambulation, exercises
• Vision	Visual aids and adaptive equipment
• Hearing	Portable amplifiers, cerumen disimpaction
• Dehydration	Volume repletion

Inouye NEJM 1999

Study Results

- Delirium reduced by 40% with absolute risk reduction 5.2%, NNT = 20
- Total number of days with delirium was reduced
- Severity of delirium and recurrence rates were **not** different
- Cost to prevent one case of delirium (in 1999) was $6,300
- Interventions which lowered risk factors were
  - Cognitive
  - Sleep Deprivation

HELP at MaineGeneral

- Target moderate to high risk patients
- Over 1100 patients seen to date
- Incidence of delirium with HELP, 3%, without HELP 12%
  - NNT 11
- Cost savings
  - LOS with delirium, 12 days
  - LOS without delirium, 5 days
  - Conservatively saving $60K per month

Drug therapy

- All drug therapy has potential side effects and all is **OFF LABEL**
- **Use only if delirium interfering with therapy, or risking patient's or others' safety and welfare**
- Almost no data on outcomes in drug treated versus non drug treated patients
- No good RCTs
- Approach based on case reports and expert opinion

Drug Therapy for Prevention

- Antipsychotics
  - "results are far from compelling and difficult to generalize"
- Acetylcholinesterase Inhibitors
  - "the routine prescription of prophylactic cholinesterase inhibitors cannot be recommended"
- Melatonin/Melatonin Agonists
  - "potential role" but "results not consistent"
  - Small studies, but favorable

Ford,A, et al. Pharmacological Interventions for Preventing Delirium in the Elderly. Maturitas 2015 (81), 287-292.

Delirium Prevention

- No difference between Spinal or General Anesthesia
  - Unless spinal patients are given very "light" sedation
- Iliac Blocks and Gabapentin before and after hip surgery may reduce post-operative delirium and decrease need for post operative opiates

Friedman, J., et al. Pharmacological Treatments of Non-Substance-Withdrawal Delirium: A Systematic Review of Prospective Trials. Am J Psychiatry 2014 (171:2).

Delirium Prevention

- Dexmedetomidine vs. Midazolam for ICU sedation
  - Significantly less delirium with Dexmedetomidine
- Melatonin vs Placebo
  - Melatonin effective at preventing delirium in some patients

Friedman, J., et al. Pharmacological Treatments of Non-Substance-Withdrawal Delirium: A Systematic Review of Prospective Trials. Am J Psychiatry 2014 (171:2).

Delirium Treatment

- Treatment of symptoms of delirium

Neuroleptics (Antipsychotics)

- Considered agents of choice for most cases of delirium
- RCTs in agitation and dementia suggest modest benefit
- Side effects can include extrapyramidal SE's, hypotension, sedation, akathisia
- Sedation effect before antipsychotic effect
- Haloperidol, droperidol
- Atypicals: Respiridone, Olanzapine, Quetiapine, Zirasidone
- **Black box warning for use in patients with Dementia**
- **All used in Delirium is "off label"**
- **Should use at lowest effective dose, with goal of use less than one week**

Neuroleptics -- continued

- Most studies were only 5-7 days duration
- No difference in outcomes Haloperidol vs Risperidone or Olanzapine
- Haloperidol showed efficacy over Lorazepam
- Avg dose of Haloperidol (1-3mg/day), Risperidone (1-3 mg/day)
- No significant EPS reported in any treatment group
- QTc changes were not measured

Haloperidol

- The most studied of ALL antipsychotics (typical/atypical) in delirium, years of use/data
- Blocks postsynaptic dopaminergic **D1** and D2 receptors in the brain→ strong central antidopaminergic → depress the CNS at the subcortical level of the brain, midbrain, and brain stem reticular formation
- Hepatic metabolism, CYP 3A4
- Onset of action: **Oral 2 to 6 hours, IM/IV 20 to 60 minutes**
- Side effects
  - EPS/Dystonia/NMS – risk much lower for IM/IV form
  - QTc prolongation – may be overstated, overall risk is small, attention if other QT prolonging meds/ >50mg in 24hrs
    - From Maldonado, J. , Critcial Care Clinics 24 (2008) 657-722
  - **Less** anticholinergic than Atypicals

Safe Use of Haloperidol

- Baseline EKG for QTc interval
- Correct K+ or Mg +2 if needed
- If Baseline QTc > 440 ms AND use of other QTc prolonging agents, use with caution
- If Baseline QTc increases by > 25% or > 500 ms, d/c Haldol
- IM preferred over IV use d/t QTc risk
- Try to avoid > 3mg/24 hours (EPS risk)
- Treat EPS with D/C med, IV benadryl
- Monitor for NMS (fever, rigidity)

Haldol -- Dosing

- Lowest possible dose, e.g., 0.5-1.0 BID tapering down as delirium clears
- IM = 0.5mg, repeat every 30 minutes until agitation is controlled (IM 2x as potent as Oral)
- Some advocate doubling of dose every 60 min (PO) or 30 min (IM/IV) until agitation is controlled
- Can be used IV - more rapid onset
  - Caution: sedation, hypotension, QTc

Atypical neuroleptics

- MOA: Dopamine (D1) and Serotonin (5HT2) Antagonism
  - Olanzapine/Quetiapine also have
    - Antihistamine (H1) = Sedation
    - Antiadrenergic (α1β) = Hypotension
    - Antimuscarini (M1) = Anticholinergic
- Risperidone has the most data, has been shown to reduce agitation in patients with dementia
- Are preferred if patient can take oral medication or if high (>3-4.5mg/day) doses of Haloperidol are required (less EPS risk)
- **All are used "off label" in delirium tx**
- Quetiapine is the preferred agent if any past hx of EPS with antipsychotics/PD/LBD , although has highest risk of hypotension/anticholinergic for atypicals
- No Studies comparing IM Ziprasadone vs IM haloperidol in delirium

Atypical Neuroleptics – Cont'd

- Risperidone : for those with side effects from haloperidol or contraindications
  - Starting dose: 0.5mg HS or BID, Inc 0.5-1 mg/day, max 6 mg/day
  - Peak 1 hour, **Half life 20-30 hours**
- Olanzapine (Zyprexa): Starting dose 2.5mg PO HS or BID, Increase by 5 mg/day, max 20 mg/day
  - Peak **6** hours, **Half Life 21-54 hours**
- Quetiapine (Seroquel) – preferred agent in PD or LBD with agitation, 12.5 mg HS or BID, Increase 12.5-25mg/day
  - Peak 1.5 hours, **Half Life 6 hours**
- Ziprasidone (Geodon) – 10 to 20 mg IM, max 40 mg/day, 10mg IM q 2 hours

Benzodiazepines

- Should usually be avoided
- Agents of choice for ETOH, benzo withdrawal
- More rapid onset than neuroleptics
- Peak effects brief, sedation more common, can prolong delirium
- Lorazepam 0.5-1 mg IV or PO (PO = $T_{1/2}$ 15-20 hours)

Patient has PD with delirium, what is the medication of choice?

Parkinson and LBD

- Psychosis is common, esp in later PD
  - Sleep disorders common
- Visual hallucination prominent in LBD
- Typical Antispychotics should be avoided
- D/C PD meds: Anticholinergics (Selegine, Amantadine), Recently added meds, Taper down to Levodopa only
- Clozapine effective with PD psychosis, ADEs
- Cholinesterase inhibitors preferred agent LBD
- Quetiapine (Seroquel) preferred agent

Take Home Points

- Delirium is an Acute Confusional State characterized by a fluctuating course and inattention
- Hospital Incidence is 5-56%, ICU 20-80%
- Neurotransmitter imbalance
- Must recognize all forms of delirium, esp **Hypoactive** (easily missed)
  - HISTORY and CAM, test of Attention
- Look for **Reversible Causes** – never just one
  - DELIRIUMS + P (pain)
- CT/EEG/LP are rarely needed
- Differentiate Delirium from Dementia based on fluctuating course and timeframe (HISTORY)
- Haldol remains the drug choice when pharamcological treatment is needed
  - Seroquel is the drug of choice for Delirium in Parkinsons/Lewy Body Dementia

Summary

Assess for risk factors (Visual Impairment, Cognition, Illness, Dehydration, Catheters, Medications)

↓

Prevention

- Environmental Pathways (Orientation, Sleep Hygiene, Early Mobility)
- Treat Dehydration/Improve Sensorium (glasses, hearing aids)

↓

Family Education on risks of development / progression of delirium (pamphlet)

↓

Assess for Delirium (**CAM and tests of Attention, History**)

↓

Look for and Treat Reversible Causes

- **DELIRIUMS + P**
- (Drugs, Ears/Eyes, Low O2, Infection, Retention, Ictal, Undernutrition/hydration, Metabolic, Sleep and Pain

Workup

- **Routine**: Vitals, O2 sat, Detailed History (cognitive, recent events), Detailed physical exam.
  - Routine LABS: CBC, lytes, BUN, Cr, glucose, calcium, LFTs, UA, EKG (consider even for baseline), CXR
  - Drug levels (Digoxin, Theophylline, Anticonvulsants)
  - Neuroimaging/CSF/EEG – rarely, for focal exam, r/o seizure/meningitis

Summary

Treatment

- Environmental (same as prevention-see above)

↓

- Look for and Treat Reversible Causes (**never just one**!!!)

↓

- Medications (Based on Severity Agitation/Threat to Self/Others)

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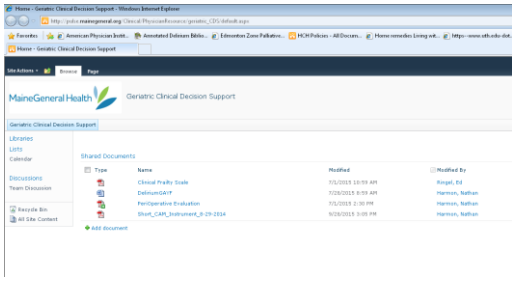
- Haldol – 0.25 to 1 mg PO, may repeat in one hour, q 4 hours max
- Haldol 0.25 to 1 mg IM (IV if needed), may repeat in 30 minutes-- may need to double dose, q 4 hours max scheduled
- Max 4.5 mg in 24 hours, d/c if increase in QTc >25% or >500, monitor for EPS
- **OR Atypicals**
- Risperdone 0.25 to 1mg HS/BID, Inc 0.5-1mg/d, max 6mg
- Olanzapine 2.5 to 10mg daily, Inc 5mg/d, max 20mg
- Quetiapine 12.5 mg HS, (most sedating/most hypotension),Inc 25mg/day, upto 100mg BID
- ***GOAL to use less than one week, taper over this time, consider discussion of long term risks/black box warnings if pt being discharged with new antipsychotic***

Parkinson/Lewy Body Dementia

- DO NOT USE HALDOL
- Quetiapine 12.5 mg HS, (most sedating/most hypotension),Inc 25mg/day, upto 100mg BID
- Lorazepam 0.25 to 1 mg PO/IV upto TID (use if hx of NMS), or if SEVERE agitation
- ***Consider Rivastigmine (Exelon)***
- ***Patch approved for PD dementia***

SCM Tools



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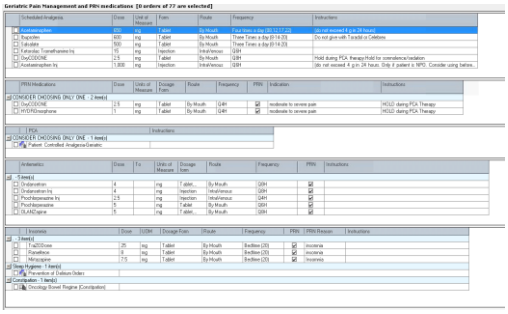

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