

Improving Outcomes With Terminal Delirium

*Could an Ounce of Prevention be Worth
a Pound of Cure?*

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Case Study 1

Mary G. is a 93 y.o. female:

- E.S. HF and cardiac cachexia, declining on the expected trajectory over several months and now approaching death.
- When you visit the home you learn that Mary has been having visions of the Devil and states that she can see him in her room.
- The visions are frightening because Mary is a devout catholic.
- Mary has been mildly confused over the last week but knows family members; she says to you "Please help me, these visions are frightening!"

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Case 1

You review Mary's meds and find that:

- Morphine sulfate 5 mg. q4h PO for pain/SOB was started 4 days ago. The family has been giving this frequently as she is increasingly dyspnic
- Lorazepam 0.5mg. Tab.1 q6h PO prn, receiving 1-2 doses per day
- Furosemide 40mg. Daily, now prn
- All other meds have been gradually withdrawn over the last few weeks as Mary is no longer able to tolerate them

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Case 1

What is your assessment :

1. Deathbed phenomenon
2. Opioid toxicity
3. Adverse reaction to morphine
4. Manifestations of religious ideation

What is your recommendation in this case?

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Case 2

Susan K. is a 67 y. o. female who has stage IV breast cancer:

- Four weeks ago she refused further chemo and signed on hospice.
- She also stopped monthly biphosphonate infusions after a final round of hemi body radiation controlled the bone pain she had from upper extremity metastatic disease.
- Susan was out to lunch with her daughters on Thursday after a morning of shopping when she developed nausea. Later that day she was noted to be lethargic and mildly confused.
- All three symptoms, nausea, lethargy, and confusion increased over 24 hours. She became irritable and restless if aroused, and refused to eat.

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Case 2

When the hospice triage line was called on Saturday the nurse informed the family that it sounded like Susan might be dying. The nurse suggested an on-call visit, continuous care, and comfort meds.

Case 2

You are the hospice nurse on call:

1. Do you think Susan is dying?
2. If not, what is your differential diagnosis?
3. What information don't you have that you badly need to evaluate and make recommendations in this situation?
4. Are labs indicated?
5. What is your assessment?

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Case 3

James B. is a 76 y.o. male with colon cancer and liver metastasis recently admitted to your hospice program.

- James is not jaundiced, but staff reports that he is "wild" and combative with the STNA. You learn that he was like this in the hospital and that is why the hospice referral was made.
- Your medical director attempts to titrate Haloperidol without success, and starts Chlorpromazine, 100mg. Q2hr., but the behaviors only get worse. It is no longer safe to keep staff in the home, and the patient refuses to leave.
- The family confides that "James has been like this a long time..."

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Case 3

Your hospice IPU refuses to take James – he was there before and left AMA, walking home in his bare feet!

All else failing, James is transported by the police to a behavioral unit at the local hospital.

Case 3

What needs to be explored?

1. James' medical, psychiatric and behavioral history?
2. Is this terminal agitation? – how would you decide
3. Is diagnostic evaluation, labs and maybe imaging, indicated?
4. Is this about cancer or your bad luck getting this patient on your service???

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Case 4

You are the palliative care nurse consultant and are asked to visit a dying patient, Wilber H. The floor nurse states that Wilber is "fine" and dying peacefully, but the wife is worried.

- Wilber, a retired farmer, 84, has lived a good life.
- Wilber has been declining from a series of mild strokes, has become very weak and debilitated; he has lived at home until pneumonia brought him to the hospital.
- Over the last week Wilber has "given up" and stopped eating.
- The pneumonia is better; Wilber has been on no meds since the IVs and antibiotics were stopped.
- Wilber is considered to be dying.

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Case 4

- When you go into the room, Wilber's wife says "please help him, I know he's not right!"
- Wilber has O2 on, appears to be sleeping, but when you speak to him he startles abruptly, and you notice that he has a "deer in the headlights" expression. You also notice that he is "picking" at the sheets and in the air with his hands.

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Case 4

1. What is your diagnosis?
2. What interventions are appropriate?
3. What do you say to Wilber's wife and the floor staff?

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Delirium

- *Probably the most distressing symptom experienced by staff and families*
- *Prevalence is high- as many as 85% of cancer patients at end of life, as many as 50% of hospitalized patients over 70 years of age, 51% of post op patients*
- *On a 0-4 scale of distressing symptoms, patients rated delirium a 3.2, families a 3.75, staff a 3.2 – all higher than pain and nausea!*

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Delirium

- *A terrible way to end a wonderful life!!*
- *We all know what it is, have a general idea what causes it, yet are unable to prevent it??*
- *Why are families and cognitively intact patients not better informed about this potentially lethal condition, what to look for, and how to alert us before the problem is advanced?*

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- *Why are supervisory staff so late to be involved when a patient becomes delirious?*
- *Why do physicians and even experienced hospice nurses often treat the condition with medications that may make it worse?*
- *The most serious and the most common psychiatric symptom experienced by patients at EOL*

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Pathogenesis of Delirium

- Poorly understood
- EEG shows diffuse slowing of cortical background activity
- Neuropsychological and neuroimaging studies show generalized disruption in higher cortical function

Pathogenesis of Delirium

- Hypotheses for pathogenesis focus on role of neurotransmitters, inflammation and chronic stress
 - Deficiency of acetylcholine (anticholinergic drugs)
 - Excess of dopamine
 - Cytokines, such as interleukin 1 and 2, tumor necrosis factor, and interferon contribute by decreasing the permeability of the blood brain barrier and altering neurotransmission

Pathogenesis of Delirium

- Chronic stress of illness:
 - Activates the sympathetic nervous system
 - Leads to increased cytokine levels
 - Hypercortisolism – which has deleterious effects on the serotonin receptors leading to delirium

Delirium – A Psychiatric Disorder

DSM IV

- Focuses on two defining features of delirium
 - Disordered attention (arousal)
 - Disordered cognition

DSM IV

Disordered attention (arousal)

A disturbance of consciousness, with reduced clarity of awareness of the environment, reduced ability to focus, sustain or shift attention

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DSM IV

Change in cognition:

Memory, disorientation, language disturbance, with no underlying dementia or pre-existing cognitive deficit

DSM IV

New classification system simplifies earlier diagnostic criteria and recognizes the importance of the *acute onset* and *organic pathology* –

- Acute onset: develops over hours to a few days, tends to fluctuate in severity during the course of the day
- DSM IV requires that there is evidence from the history, physical or laboratory findings of a medical condition judged to be etiologically related to the disturbance

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Differential Diagnoses

- Dementia – fixed deficit that develops over a specific interval of time and is progressive and irreversible
- Depression – can mimic dementia when severe enough, hypomanic delirium may be confused with depression
- Psychotic mood disorders
- Delirium superimposed on dementia

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Delirious States We See Every Day

- “Sundowners” – delirium superimposed on dementia
- Acute alcohol or drug intoxication
- Febrile illness with delirium

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Sub Groups of Delirium

In order to treat, we need to describe: Three subgroups of delirium help us to describe to others what we are seeing: –

Hyperactive:

Characterized by hallucinations, delusions, agitation, disorientation

- Hypoactive
 - Characterized by confusion, sedation
- Mixed
 - Characterized by alternating features of hyper and hypo active delirium

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Sub Groups of Delirium

- *Studies suggest that the different sub groups of delirium may be related to specific etiologies of delirium, may have differing pathophysiologies, and may have differential responses to treatment!*
- *As many as 2/3 cases of delirium are either hypomanic or mixed; therefore, the ones we most often identify, the hyperactive agitated, delirious patient may actually be a minority of the occurrences!*

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Assessment Tools

- Mini mental status exam (MMSE) – screens for cognitive decline but does not distinguish between delirium and dementia.
- Delirium Rating Scale Revised 98: reliable, clinician assessment rating tool
- Confusion Assessment Method (CAM)

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Assessment Tools

- Abbreviated cognitive rating test for delirium – designed for ICUs
- Memorial delirium assessment scale (MDAS) – validated among hospitalized patients with advanced cancer and HIV

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Etiologies of Delirium in Advanced Disease

- Medication related
- Infectious etiologies
- Paraneoplastic syndromes
- Fluid and electrolyte imbalances
- Hypoxia
- Metabolic encephalopathy
- Organ failure –heart/lung/renal
- Chemotherapeutic side effects

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Etiologies of Delirium in Advanced Disease

- Tumors of the CNS/seizures
- Blood disorders
- Nutritional disorders and deficiencies
- Withdrawal of medications
- Breakdown products of tumor necrosis – tumor necrosis factor, others

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Of all the etiologies, most common is medication reactions

- Opioids
- Benzodiazepines
- Antihistamines
- SSRIs – (withdrawal of Paroxetine)
- Steroids
- Floxin antibiotics
- Anticholinergic medications

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Etiologies of Delirium

- Three take home points, from the literature:
 - *Almost all delirium is multifactorial.*
 - *Medications are almost always involved, either as the causative etiology, or are aggravating other etiologies.*
 - *In Hospice and palliative care, at EOL, terminal delirium is largely about meds, organ failure and tumor breakdown!*

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Serotonin Syndrome

EOL Care – Is All Delirium “Terminal”??

- *Assuring that we not confuse dying with a reversible delirium: Serotonin syndrome*

Little recognized, 85% of physicians are unaware of Serotonin Syndrome!!

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Serotonin Syndrome

Caused by an excess of body serotonin due to serotonergic medications, many are medications frequently used in HPM:

- SSRIs – paroxetine, citalopram, fluoxetine
- TCAs ,buspirone, venlafaxine, MAO inhibitor
- Neuroleptics – olanzapine, risperidone
- Opioids fentanyl, meperidine, tramadol, pentazocine
- Antibiotics- floxins
- Antiemetics – ondansetron, metoclopramide
- OTCs – dextromethorphan, herbals, St John's wort

Serotonin Syndrome

EOL Care – Is All Delirium “Terminal”??

- *Assuring that we not confuse dying with a reversible delirium: Serotonin syndrome*

- Characterized by
 - autonomic instability: diarrhea, fever, variations in vital signs
 - neurological: mydriasis, hyperreflexia, clonus, akathisia
 - Cognitive changes: Delirium to coma

Abrupt onset, but more likely to occur in advanced disease states, often noted to occur after the addition of a new serotonergic medication or after an increase in the dose of a serotonergic medication

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Serotonin Syndrome

REVIEW THE MED PROFILE!!

A patient with three or more serotonergic medications, recent addition of a new serotonergic medication or increase in the dosage of one, with new onset of unexplained delirium, may have this syndrome.

Treatment is to stop the serotonergic medications, delirium will reverse itself.

Opioid Toxicity Syndrome

Assuring that we not confuse a reversible delirium with dying- -

- Opioid toxicity – caused by central excitation of neural pathways when opioid doses are escalated rapidly over a brief period of time without improvement in pain control and often with onset of new and increased pain.
- Often other medications and organ failure are contributing factors in a situation of advanced or complex illness.

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Opioid Toxicity

- Characterized by
 - myoclonus,
 - agitation,
 - delirium,
 - hyperalgesia,
 - allodynia
 - add a neuroleptic,
 - treat delirium

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Opioid Toxicity Syndrome

- Treatment
 - Rotate opioids
 - Decrease the total opioid load markedly – by as much as 75%
 - Add a neuroleptic – such as gabapentin
 - Treat delirium

Opioid Toxicity

Assuring that we not confuse a reversible delirium with dying –

Often occurs when onset of terminal delirium is mistaken for a pain crisis and continual and repeated increases in pain meds leads only to increased agitation and increased pain behaviors.

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Not to Confuse Reversible Deliriums with Dying -

- Neuroleptic malignant syndrome
- Paraneoplastic syndromes – hypercalcemia, SIADH
- Anticholinergic Syndrome - look for mydriasis
- Hypothyroidism

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Non Convulsive Status Epilepticus

- Patients may be delirious as a result of acute encephalopathy secondary to repeated seizures.
- Etiology: complex metabolic abnormalities, brain tumor, CVA/TIA
- Treatment: anticonvulsants

End Organ Failure Associated Delirium

- Hepatic Encephalopathy
- Delirium superimposed on dementia – Sundowners, agitated behaviors
- Renal failure with episodic delirium

These can present as the etiology of terminal delirium or as a component of the processes we manage in providing care.

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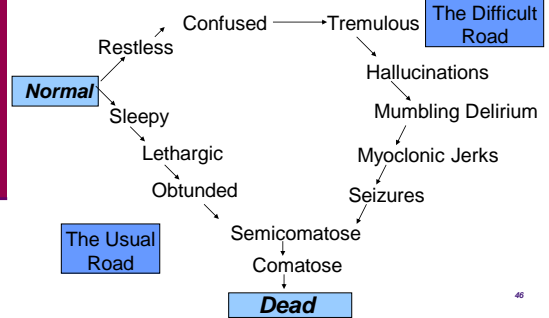
Approach to Management of Delirium in EOL Care

- Delirium is a terrible prodromal to dying: it is imperative that we provide our expertise in this disastrous condition.
- Hospice and palliative care providers are the experts in delirium, just as we are the experts in the management of almost all other EOL Symptoms: dyspnea, pain, nausea and vomiting.

We need to approach delirium as a treatable condition, that needs to be resolved to whatever extent possible so that our patients can die comfortably.

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Two Roads to Death



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Approach to Management

When is it appropriate to evaluate the etiology of the dementia?

"When confronted with a diagnosis of delirium in a terminally ill patient, a differential diagnosis should always be formulated."

Page 1417, Oxford Text of Palliative Care, 4th edition, 2009

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Approach to Management

Five steps:

1. Develop a differential diagnosis, that is, search for the underlying cause, r/o reversible delirium
2. Identify the subtype of this patient's delirium: hypoactive, hyperactive or mixed?
3. Investigate, substantiate and document your impression on diagnostic or clinical grounds
4. Resolve resolvable symptoms
5. Manage symptoms that can't be resolved

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Approach to Management

The patient's position on the trajectory of the illness is the most important factor to consider in determining the approach to care:

- Is this patient dying? How do I know?
- Did I expect this to happen to my patient now or is something wrong here?
- Lets talk it over.....

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Approach to Management

- Goals drive care – *always*
- What are the goals of care for this patient at this time?
- An etiology is determined in less than 50% of cases that are actually evaluated.

Drug related causes are the most likely to be reversible or improved by interventions.

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Approach to Management Non-pharmacological Interventions

- Bowels - note patients posturing, more likely to cause pain behaviors than agitation
- Bladder, extremely common cause of agitation in the last days of living- especially in older men

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Non-Pharmacologic Interventions

Urinary retention –

- All opioids cause urinary retention
- Cachectic patients may have a full bladder which is not palpable

If retention is the cause of agitation, once the bladder is emptied the patient will go off to sleep, and die peacefully!

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Non-Pharmacologic Interventions

- The hyper-vigilant family
- The over stimulating environment: room should be mellow but not dark, remove scary items and don't show war movies
- Music, aroma therapy, pictures
- Clothing, armbands,
- Families differ: "Dad loved a party, he would be glad we are having one!" Take your clue from the patients response to what is going on around him or her

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Pharmacologic Management

- Haloperidol: why is it in the comfort kit when all we need is Ativan?!!

Haloperidol - A neuroleptic drug that is a potent dopamine blocker

- The drug of choice for treating delirium in patients with advanced disease
- Has a wide range of dosing in EOL car
- Can be given SQ, PO, SL, IM, PR

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Haloperidol

- Parenteral doses are twice as potent as oral and much more rapid acting –SQ,IM,IV.
- Concerns with Q wave prolongation occur only with IV administration of very high doses
- Concerns for extra pyramidal side effects if used early in the clinical course – not a medication for long term use
- An excellent emetic: the first line drug for chemoreceptor trigger zone induced nausea and vomiting in EOL patients (metabolic and drug induced nausea)

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Haloperidol

Doses vary widely between practitioners: common ranges may be up to 20mg./day, but doses greater than 250mg/day IV have been used!

Page 1474, Oxford Textbook of Palliative Care, 4th edition

Management of Hypoactive Delirium

- Evaluate the medication profile
- Start Haloperidol in low doses:
 - Titrate as needed: a typical regimen is 0.5mg of haloperidol q1hr till calm, determine a RTC dose based on need, expectation is that patient may need 1-3mg/day
 - If sedation is needed, add a low dose of an anxiolytic, such as lorazepam 0.5mg 2-3x per day depending on the age of the patient and previous drug use and history.

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Treatment of Hypomanic Delirium

If prns orders for haldol and lorazepam are given to staff, the order should read to "use Haloperidol for delirium, use Lorazepam if not resting, limit the # of does of prn benzodiazepine permitted in a 24 hr period.

Approach to Management: Hyperactive Delirium

"Dad was dying peacefully but for the last three days we can't keep him in bed, he is swinging at my brother and no one has slept!!"

Why do we get this call so late?

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Management: Hyperactive Delirium

- Haldoperidol 2mg P.O stat and repeat q 1hr until calm
- Lorazepam 1mg. p.o. stat and 0.5mg. p.o. 2-3 x/day – no prns
- Once calm, add up the total dose of Haloperidol required to calm patient and divide into RTC doses q4- 6 hrs with a prn of 2mg. Q2hrs prn., call doctor if patient not calm after 2 prn doses in 4 hours
- Start continuous care

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Hyperactive Delirium

“Doctor, the haldoperidol isn’t working”
Oh, no!

Check to see what we missed? Drugs d/c’ d, psychosocial issues, the bowls, the bladder, the hypervigilant family, the hyper stimulating environment - the unfinished business?, existential concerns?

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Hyperactive Delirium

- Chlorpromazine 12.5- 50mg q4-12 hrs PO, IM, IV, PR
- Start with a loading dose of 50 mg IM or PO stat and repeat q 1 hour till calm; determine a RTC dose based on the total dose needed to calm the patient and give q6hrs with a break thru dose q2hr, call doctor if 2 break thru doses in 4 hours and patient not resting
- This patient is non-ambulatory d/t the hypotensive side effects of chlorpromazine, but, of course, that’s the goal – sleeping!
- Once symptoms are controlled, gradually lengthen the interval between RTC doses in hopes of improving the level of consciousness if that is an appropriate goal.

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Hyperactive Delirium

- Called the “abnormal road to death”
- Patients are often on the “normal road” to death when they develop the delirium.
- The goal is to put them back on the normal road.
- Families need to be informed that once the patient is calm again, it is expected that they will be sleeping and will be dying, families appreciate this information and tend to understand.

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Terminal Sedation for Terminal Delirium

“10-20 percent of patients with hyperactive terminal delirium can only be controlled with medications to the point of sedation to a significantly reduced level of consciousness.”

- Inpatient setting, hospital or IPU:
midazolam,30-100mg/24 hr IV
- At home, chlorpromazine IM/PR may be the drug of choice if venous access is not available

Oxford Text of Palliative Care,
4th edition, P 1475

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In Hospital Palliative Care Approach to Delirium

- Delirium is more likely to be recognized earlier in the hospital setting.
- Delirium is more likely to be evaluated by lab or imaging.
- Potentially reversible delirium is more likely to be reversed.
- Hydration is more likely to be a treatment modality.
- True “terminal delirium” is not reversible, but hyperactive delirium may be improved with hydration, which may also prolong the process of dying.

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Hospital Management of EOL Delirium

- The same medications and regimens are appropriate but the route of administration is more likely to be parenteral.
- Patients arriving at the hospital in a state of hyperactive delirium are apt to have a very poor outcome if a palliative care professional is not available to care for them.
- Hypoactive delirium may not be recognized in the hospital just as it may not be recognized in the home or nursing home.

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Special Situations

- Parkinson’s Disease – Quetiapine 25 – 200mg q12-24 hr, PO/PR
- Delirium superimposed on dementia: “Sundowning” a typical antipsychotic, risperidone 1-3 mg, q12-24, with or without valproic acid 250mg-2000mg daily
- Hyperactive delirium in the patient with hepatic encephalopathy – will likely require Chlorpromazine

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Special Situations

- Renal failure –
 - Opioids of choice: methadone, fentanyl first line choice if accessible
 - Oxycodone, hydromorphone - second line choice
 - Morphine sulfate – increase the interval between doses, start haloperidol proactively as death is approaching, especially ES renal failure stopping dialysis

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Why don't we do better?

- Impediments to improved outcomes:
 - Communication barriers with our hospice doctors and attending physicians?
 - Why do we call and say the patient is "agitated" or "restless" when we should be saying: "doctor this patient is delirious!"

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Delirium – why don't we do better?

- ***Failure of consistency in utilizing diagnostic classification system to properly evaluate and document delirium***

Why don't we do better -

Polypharmacy - endemic in our practice of palliative care as well as the practice of medicine

Delirium – Why don't we do better??

- The syndrome of "NOTS"
 - Not well recognized
 - Not well communicated
 - Not well managed

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Why don't we do better?

The disconnect between on-call staff and the patient's PCRN: *would the PCRN be surprised to learn her patient was dying?*

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How might we do better?

- Recognizing that our patients have fragile brains
- Recognizing the warning signs and symptoms of delirium earlier in the course
- Informing and educating families about delirium, what it is and what to look for

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Early Warning Signs

- Change in mood in a patient previously stable
- Burst of energy: "Dad has more energy again – he was out mowing the lawn last night but he is resting now"; "Mom always liked to cook so last night she made brownies."
- Inappropriate behaviors
- Day/night reversal and change in sleep patterns

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Early Warning Signs

These stories should alert the clinically savvy HPM nurse to do a complete assessment to look for symptoms of change in cognitive or a disturbance in the level of consciousness

Early warning signs: review the med sheet – is there a new med, a change in dose, or a medication that has been d/cd?

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Would early intervention be appropriate?

- Changing meds we know to be problematic?
- Rotating Opioids?
- Reducing the use of morphine sulfate, especially in the elderly
- Remembering that as patients are not eating and drinking their renal functions are declining and as the renal function declines, should we increase the interval between doses of implicated medications?

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Remember:

- “Doctor, my patient is DELIRIOUS!!!”

(The nurse may be anxious or agitated but the patient is delirious!)

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“Doctor, my patient is delirious

- Delirium is a diagnosis- can nurses diagnose?
- Is Delirious an adjective, or a diagnosis?
- If you have utilized a tool to evaluate for delirium, that is within nursing scope of practice and you can share the results of your evaluation with the doctor,
 - i.e. “on the MDRS, the pt meets criteria for Delirium, can I review my clinical findings with you?”

At the end of the day –

“Slowly I learn about the importance of powerlessness. I experience it in my own life, and I live with it in my work. The secret is not to be afraid of it, not to run away. Patients know that we are not God... All they only ask is that we do not desert them.”

Cassidy, S. *Sharing the Darkness*. London: Darton, Longman and Todd, 1988

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*"YOU MATTER BECAUSE YOU ARE YOU.
YOU MATTER TO THE LAST MOMENT
OF LIFE, AND WE WILL DO ALL WE CAN,
NOT ONLY TO HELP YOU TO DIE
PEACEFULLY, BUT ALSO TO LIVE
UNTIL YOU DIE."*

*Dame Cicely Saunders
St. Christopher's Hospice, 1967*

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