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First Do No Harm . . . Terminal Restlessness or Drug-Induced Delirium

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ABSTRACT

Terminal restlessness is a term frequently used to refer to a clinical spectrum of unsettled behaviors in the last few days of life. Because there are many similarities between the clinical pictures observed in terminal restlessness and delirium, we postulate that at times what is referred to as terminal restlessness may actually be an acute delirium sometimes caused by medication used for symptom control. It is important therefore to consider the causes for this distressing clinical entity, treat it appropriately, and ensure the treatment provided does not increase its severity. This brief review aims to consider the medications that are commonly used toward the end of life that may result in a picture of delirium (or terminal restlessness). These include opioids, antisecretory agents, anxiolytics, antidepressants, antipsychotics, antiepileptics, steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). This review also aims to raise awareness regarding the recognition and diagnosis of delirium and to highlight the fact that delirium may be reversible in up to half of all cases. Good management of delirium has the potential to significantly improve patient care at the end of life.

INTRODUCTION

TERMINAL RESTLESSNESS is a term frequently used to refer to a clinical spectrum of unsettled behaviors in the last few days of life. Many other terms including terminal anguish, terminal agitation, and predeath restlessness have been used to describe this clinical state. The symptoms of terminal restlessness include irritability, anxiety, unease, distress, inattention, hallucinations, and paranoia. The signs include restlessness, fidgeting, purposeless yet coordinated movements, tossing and turning, trying to get out of bed, moaning, grimacing, jerking, twitching, myoclonus, confusion, picking at sheets, cognitive impairment and aggression. In one study the prevalence of terminal restlessness was 42% in the last 48 hours of life.[1]

Delirium is a condition with specific diagnostic criteria, characterized by acute onset, altered level of consciousness, fluctuating course and disturbances in orientation, memory, thought, and behavior.[2] Delirium is associated with increased levels of mortality,[2,3] with papers quoting mortality rates ranging from 10% to 65%.[4] Table 1 outlines the criteria used for diagnosing delirium according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.[3,5,6] Delirium is often underrecognized or misdiagnosed as other psychiatric conditions and therefore undertreated.[3,7] Although the earliest symptoms of delirium are neuropsychiatric, other nonspecific symp-

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TABLE 1. CRITERIA FOR DIAGNOSING DELIRIUM (DSM-IV)

1. Disturbed consciousness with reduced ability to focus, sustain or shift attention
2. Change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a new perceptual disturbance
3. Acute onset (usually hours to days) and a fluctuating course.
4. Evidence of a physical (organic) cause.

toms should raise concern that delirium is present—the frail elderly may manifest decreased food intake and decreased activity.[5]

Because there are many similarities between the clinical pictures observed in terminal restlessness and delirium, we postulate that at times what is referred to as terminal restlessness and considered to be a common, if unwanted, part of the dying process, may actually be a potentially reversible acute delirium.

Lawlor et al.[8] studied the occurrence, precipitating factors, and reversibility of delirium in patients with advanced cancer. The study found that delirium was reversible in 49% of episodes and that terminal delirium occurred in 88% of deaths. In univariate analysis, psychoactive medications, predominately opioids, and dehydration were associated with reversibility. In multivariate analysis, psychoactive medications, hypoxic encephalopathy, and nonrespiratory infection had independent associations. Lawlor et al.[8] concluded that despite its terminal presentation in most patients, delirium is reversible in approximately 50% of episodes, and delirium precipitated by opioids and other psychoactive medications is frequently reversible with changes in opioid, dose reduction, or discontinuation of unnecessary psychoactive medications.

It is important therefore to consider the causes for this distressing clinical entity, treat it appropriately, and ensure the treatment provided does not increase its severity. Many of the drugs used when approaching the terminal phase are reported to cause delirium. There is little written about drug-induced causes of delirium in palliative literature. Much of the published material has come from geriatric, anesthetic, and psychiatric settings and can be applied in the palliative setting. This brief review aims to consider the medications that are commonly used towards the end of life that may result in a picture of delirium (or terminal restlessness).

TYPES OF DELIRIUM

Delirium is not a homogeneous syndrome and has different subtypes.[9] The most commonly used classification of delirium subtypes is that proposed by Lipowski.[10] He described three different subtypes based on psychomotor activity or alertness: hyperactive–hyperalert (or agitated), hypoactive–hypoalert (somnolent), and a mixed delirium.

In the hyperactive–hyperalert variant, patients may range from being fidgety or restless to being verbally and physically aggressive. Hallucinations and delusions are most common in hyperactive delirium. In the hypoactive–hypoalert variant patients range from being lethargic and quiet to stuperous, in which they can only be aroused by vigorous and repeated stimuli. In the mixed variant many patients alternate unpredictably between a hyperactive–hyperalert and a hypoactive–hypoalert pattern of delirium, either during a single day or over the course of a few days and changes of this type may be interpreted as a major change in the underlying clinical condition.[9]

PREDISPOSING AND PRECIPITATING FACTORS

Delirium, especially in older patients, is usually multifactorial in origin. There is an inverse relationship between the severity of the insult necessary to precipitate delirium and the preexisting vulnerability of the patient.[11] Risk factors for delirium can therefore be categorized according to whether they are predisposing or precipitating factors.[3]

One predisposing factor is age. There is a significant increase in the prevalence of delirium with increasing age: 0.4% in those over 18 years old, 1.1% of those over the age of 55, and 13.6% in those over 85.[3] Other predisposing factors (baseline patient characteristics) include male gender, visual impairment, previous dementia (especially if severe), depression, functional dependence, immobility, hip fracture, dehydration, alcoholism, severity of physical illness, stroke and metabolic abnormalities.[3,4]

Precipitating factors include infection, metabolic disturbances, hypoxaemia, anemia, urinary retention, bladder catheterization, fecal impaction, alcohol withdrawal, surgery, psychosocial factors, and drugs.[3,4] Nearly any drug can

cause cognitive impairment in susceptible individuals; however, certain classes such as opioids, anticholinergics, and benzodiazepines are commonly implicated.[4]

Many patients approaching the end of life therefore have multiple predisposing factors to delirium, and it is important to minimize the precipitating factors whenever possible.

PATHOPHYSIOLOGY

Insight into the mechanism by which some medications contribute to delirium can be gained by understanding the etiology of delirium. Delirium is marked by a global cerebral dysfunction resulting in a generalized reduction in cerebral oxidative metabolism and an imbalance of several neurotransmitters.[4,11,12] Any drug that interferes with neurotransmitter function or with the supply or use of substrates for metabolism can cause delirium.[12]

Neurotransmitter pathways act and interact at many areas throughout the brain, and none of the clinical characteristics of delirium can be solely attributable to the disturbance of a single pathway.[9] However, many lines of evidence support the hypothesis that delirium is mediated in part by a failure in central cholinergic transmission, a major system that regulates arousal, attention and memory process.[4] Data from animal and clinical studies support the hypothesis that acetylcholine is one of the critical neurotransmitters in the pathogenesis of delirium, and it may be that acetylcholine serves as the final common neurotransmitter pathway.[13] The administration of anticholinergic substances to both experimental animals and humans results in the characteristic manifestations of delirium including specific electroencephalogram (EEG) changes.[14] This may be an oversimplification, however, because other neurotransmitters, including serotonin, noradrenaline, dopamine and gamma-aminobutyric (GABA) have also been implicated in the pathogenesis of delirium.[12] Flacker and Lipsitz[14] proposed that there is probably no final common pathway to delirium, but that delirium should be thought of as the final common symptom of a variety of situation-specific neurotransmitter abnormalities.

There is additional evidence to support a role for cholinergic deficiency in delirium. First, risk factors for delirium include metabolic and structural brain abnormalities associated with decreased acetylcholine activity. Second, high serum anticholinergic activity is associated with the severity of the delirium. Third, there is anecdotal evidence to suggest that anticholinesterase drugs used in the treatment of Alzheimer's disease may also be of good benefit in treating the symptoms of delirium.[3] The impact of acetylcholine is also supported by studies that show that acetylcholine neurotransmission decreases with age, which supports that increasing age is a consistent risk factor for delirium.[13] The centrally acting cholinomimetic agent physostigmine salicylate has been used to treat anticholinergic delirium since the mid-1800s, and conversely hyoscine hydrobromide, a powerful anticholinergic drug, has been used to induce and study these confusional states experimentally.[15] A study in Finland demonstrated that cerebrospinal fluid (CSF) acetylcholinesterase levels measured in acute delirium correlated with the length of life after delirium suggesting that cholinergic dysfunction may also have prognostic significance in these patients.[16]

Neuroimaging studies suggest that disruption to the frontal cortex, anteromedial thalamus, right basal ganglia, right posterior parietal cortex and mesial-basal temporooccipital cortex is particularly important. This is consistent with models of delirium that involve disruption of attentional systems in the brain, including those responsible for arousal.[17]

COMMONLY USED DRUGS IN PALLIATIVE CARE THAT CAUSE DELIRIUM

A variety of drugs have been reported to induce delirium, and drug-induced delirium is common. In studies of elderly hospital patients, drugs have been reported as the cause of delirium in 11%–30% of cases.[12] The relationship of drugs to delirium is most clear for anticholinergic drugs with muscarine receptor affinity,[18] and there have been over 600 drugs identified with anticholinergic effects. Anticholinergic delirium is characteristically associated with agitated behavior and florid visual hallucinations, however, signs of peripheral autonomic anticholinergic toxicity may or may not be present.[12]

All drugs with pure anticholinergic activity such as hyoscine hydrobromide will in suffi-

ciently high doses induce delirium, especially in susceptible individuals and are therefore considered as high risk. To this high-risk group also belong some other drugs which, with regard to the ability to induce delirium, behave like anticholinergic drugs. Other drugs, like benzodiazepines, will induce delirium, but less frequently and therefore are classed as medium risk. Some drugs are very seldom associated with delirium and constitute a low risk group.[18] Central nervous system (CNS) toxicity can occur in a dose-dependent manner, often as a result of interference with neurotransmitter function. Drug-induced delirium can also occur as an idiosyncratic complication[12] or as unforeseen side effects of prescribed medication, and can be contributed to by metabolites of drugs not usually thought of as having major anticholinergic effects.[11] Anticholinergic drugs with less ability to cross the blood–brain barrier have a lower tendency to produce delirium.[18]

For a drug to be clearly implicated as a cause of delirium, its administration should precede the onset of symptoms within a short time span (usually hours to days) and withdrawal of the drug should lead to a return to baseline cognitive functioning.[12]

Below are discussed some drugs that are commonly used near the end of life and have been implicated in causing delirium.

Opioids

Opioid use was associated with delirium in 3 of 5 large prospective studies of hospitalized patients.[4] Opioids will often induce delirium in aged or demented patients, with codeine and dextropropoxyphene inducing delirium a little less often than other analgesic drugs. However, the risk of delirium associated with opioids is dose related.[18] Kuzuma et al.[19] reported a case of a 14-year-old boy with acute toxic delirium. He had been treated for several months with transdermal fentanyl, and when the dose was increased he became delirious. They concluded that if central nervous excitatory symptoms develop in a patient treated with transdermal fentanyl, after other causes of delirium have been excluded, consideration should be given to removing the patch and opioid rotating.[19]

There is experimental evidence that some opioid analgesics reduce the release of acetylcholine in the cerebral cortex, and dose dependent binding to muscarinic receptors in the brain has been demonstrated with fentanyl.[20] Oxycodone has also been demonstrated to have anticholinergic effects.[13] Therefore changes in an opioid or an increase in a dose prior to the onset of a delirium picture should be considered as a possible cause and appropriate measures taken (Table 2).

Antisecretory medication

Hyoscine hydrobromide (scopolamine) and glycopyronnium (Robinul) are both anticholinergic drugs that are commonly used for the treatment of terminal secretions (or death rattle). Unlike glycopyronnium, hyoscine hydrobromide crosses the blood–brain barrier. It therefore has central anticholinergic effects resulting in drowsiness, hypnosis, amnesia, and occasionally coma. However, it may cause agitation, delirium, excitement and hyperpyrexia due to an absolute or relative reduction in cholinergic activity in the central nervous system (CNS), possibly due to an antagonistic effect to arousal at a hypothalamic and brainstem level.[21] Hyoscine hydrobromide, even at very low doses, is commonly associated with cognitive changes, including hallucinations and overt delirium.[12] Hyoscine hydrobromide can be used topically as a transdermal patch or subcutaneously by injection or syringe driver. In a case report from the anaesthetic setting, Wilden and Rapeport[21] suggested reducing the use of anticholinergic premedication and advocated the increased use of glycopyrrolate which does not cross the blood brain barrier and therefore is unlikely to cause central effects. The use of glycopyronnium should lead to a lower incidence of the anticholinergic problems which were often seen in anesthesia. As these drugs are commonly used in the palliative setting, it may be possible to draw a similar conclusion.

Anxiolytics

Although most patients become sedated after receiving benzodiazepines, it has been well documented that benzodiazepines can infrequently cause paradoxical hostility, aggressiveness, confusion, and agitation. The etiology of these paradoxical reactions is unknown, although it has been postulated that benzodiazepines alter the levels of multiple CNS neurotransmitters including catecholamines, serotonin, and acetylcholine, resulting in disinhibitory behavior in susceptible

TABLE 2. DELIRIUM INDUCING DRUGS COMMONLY USED IN PALLIATIVE MEDICINE

Opioids	e.g. morphine (M S Contin, Oramorph SR, Roxanol), fentanyl (Actiq, Duragesic, Sublimaze), oxycodone (OxyContin, Oxydose, Percolone, Roxicodone)
Anti-secretory Medication	e.g. hyoscine hydrobromide (injection, Scopolamine—transdermal) [see text], Atropic drops
Anxiolytics	e.g. midazolam (Versed), diazepam (Valium), lorazepam (Ativan) [see below]
Antipsychotics	Antipsychotics, especially those with an anticholinergic effect, can induce delirium, and all traditional antipsychotic drugs have been reported to increase the risk of delirium. Methotrimeprazine (Levomepromazine/Nozinan) which is a frequently used anti-emetic, has considerable anticholinergic properties and therefore presents a high risk of inducing delirium.[16]
Antidepressant Drugs	All tricyclic antidepressant drugs exert an anticholinergic effect, with amitryptiline (Elavil, Endep) having the strongest and nortriptyline (Aventyl, Pamelor) the weakest. The tricyclic antidepressants constitute a high risk group of drugs.[16]
Anti-epileptics	All antiepileptics have been reported to induce delirium, although the mechanisms are undertain with probable differences between the different drugs.[16]
Steroids	Adverse CNS effects associated with corticosteroid therapy include delirium and chronic cognitive impairment, the risk being dose related.[10]
NSAIDs	All non steroidal anti-inflammatory drugs have been reported to induce delirium.[16]

patients.[22] The reversal of benzodiazepine-induced somnolence with the cholinergic-activating drug physostigmine suggests that the benzodiazepines reduce cholinergic function, which would imply a mechanism. Benzodiazepines can therefore induce delirium and the elderly seem to be more sensitive to these side effects. Benzodiazepines have varying potency to cause delirium, but all should be regarded as medium risk drugs.[18] A study in postoperative patients found that long-acting benzodiazepines and higher dose exposure showed a trend toward a stronger correlation with delirium than did short-acting benzodiazepines, and-low dose exposures.[23] Midazolam has repeatedly been shown to be associated with anterograde amnesia[24–26] that is likely to negatively influence cognitive assessment particularly in relation to orientation in time and place. Paradoxical reactions may be dose dependent and more prevalent in stressful situations, and may occur in patients who have previously taken benzodiazepines without ill effects.[22]

Interactions between medications

Problems with side effects increase considerably when a patient is given several drugs, with additive effects and prolonged half-times being common.[18] Polypharmacy often makes it difficult to identify a single causative drug. A study by Patten et al.[27] found that lithium, anticholinergics, and antipsychotics were all significantly associated with the occurrence of delirium, and the effects were multiplicative with no evidence of interaction between the medication exposures.

Management

A comprehensive history, physical examination, and relevant investigations are mandatory. The neurologic and mental status examination should focus on the features of delirium and any signs of focal neurologic deficits. The medication history is crucial,[5] usually from a family member or from other medical or nursing professionals, as drug-induced delirium is generally treated conservatively by withdrawing the offending agent.[28] The dose should at least be reduced if withdrawal is not possible.[4] Neurologic and mental state status should be assessed.[7] Blood investigations should assess electrolytes (hypernatremia/hyponatremia, hypercalcemia), renal function (dehydration, renal failure), white cell count (infection), and thyroid function (hypothyroidism/hyperthyroidism). Pulse oxyimetry may reveal hypoxia.

Prevention is better than cure, and so the general principle to minimize the occurrence of delirium is to avoid medications likely to induce it if alternative medications exist, and to use the lowest effective dose possible. If possible, low-risk drugs should be used and if drugs with a high risk of inducing delirium are used, the patient should be observed for a longer period in order to detect adverse reactions.[4,18]

A randomized trial,[29] albeit in younger patients with acquired immune deficiency syndrome (AIDS), has confirmed that neuroleptic agents are superior to benzodiazepines for control of the symptoms of delirium because they do not impair respiratory function and are less likely than benzodiazepines to cause drowsiness or disinhibition.[11] Haloperidol remains the standard treatment; it is a powerful antipsychotic that can be given orally or parenterally and has limited anticholinergic, sedative, hypotensive, or proarrhythmic properties.[11,28,30] Neuroleptic agents can however cause other neuropsychiatric problems such as akathisia.[31] The neuroleptic agents ameliorate a range of symptoms and are effective both in patients with a hyperactive or hypoactive clinical profile.[28]

Physostigmine (a cholinergic agonist) is known to be helpful in the treatment of delirium caused by anticholinergic toxicity, but its use has been limited by peripheral cholinergic (parasympathetic) toxicity including excessive respiratory tract secretion, emesis, diarrhea, and cardiac dysrhythmia.[14] It crosses the blood brain barrier and therefore reverses the central effects of anticholinergic drugs.[12] Trials are investigating whether cholinesterase inhibitors such as donepezil may be useful in treating (or preventing) delirium.[11] Serotonin antagonists such as trazodone may also be helpful.[3]

Benzodiazepines are the first-line treatment for delirium that is associated with seizures or withdrawal from alcohol or sedatives. They are also a useful adjuvant treatment for patients who cannot tolerate antipsychotic drugs. Benzodiazepines can therefore both protect against delirium and be a risk factor for it.[28]

CONCLUSION

Terminal restlessness may be caused by an acute delirium that is a potentially reversible condition in up to half of patients who develop it. Causes, especially those that are drug-induced, should be sought and treated when appropriate. When a patient is in the terminal phase, it is important to avoid inducing agitation by the drugs given to promote comfort. The drugs given to patients in the later phases of illness may actually cause delirium that can be misinterpreted in the palliative care setting as terminal restlessness. Therefore, if a patient does become unsettled after a potentially causative drug has been administered, a change in the medication should be considered, and the potentially causative drug should not be given again if possible. Hydration and opioid rotation should also be considered.[8,30]

Educational strategies in palliative care aimed at raising awareness of neuropsychiatric disorders, including delirium, should be developed. Nonrecognition and misdiagnosis of delirium appear to be common.[30] It is important for optimal patient care that suspected terminal restlessness is not simply assumed to be irreversible and the patient sedated, without due consideration being given to possible causes, including the medications outlined in this paper. If the cause is found and treated, the clinical symptoms of delirium that are distressing for the patient, family members, and staff are more likely to be adequately controlled.

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Delirium at end of life

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Delirium

- What is it?
- Why is it important?
- What causes it?
- How do you manage the patient with delirium near the end of life?

Delirium

What is it?

Q: Delirium is experienced in up to what percentage of terminally ill cancer patients?

1. 10%
2. 23%
3. 50%
4. 85%

Q: Which symptom is characteristic of delirium?

1. impairment of only short term memory
2. impairment of attention
3. agitation or restlessness
4. delusions or hallucinations

Early Descriptions

- Hippocrates:400 BCE
  - "they move the face, hunt in empty air, pluck nap from the bedclothes...all these signs are bad, in fact deadly"
- Celsus: 1st Century CE
  - "Sick people...lose their judgement and talk incoherently...when the violence of the fit is abated, the judgement presently returns...

Synonyms

- Acute confusional state
- Acute mental status change
- Altered mental status
- Organic brain syndrome
- Toxic/metabolic encephalopathy
- Reversible dementia

Subacute befuddlement

Synonyms

- Agitated
- Confused
- Combative
- Restless
- Crazy
- Lethargic

Out of it

- Out to lunch
- Poor historian
- Seeing things
- Sleepy
- Uncooperative
- Wild man

Terminal Agitation

A Symptom or Sign: thrashing or agitation that may occur in the last days or hours of life

Broad differential, including:

- Pain
- Anxiety
- Dyspnea
- Delirium

Delirium

- *Delirare*: to be crazy
- *De lira*: to leave the furrows

DSM-IV Criteria: Delirium

- Disturbance in consciousness
  - Attention
- Change in cognition
  - eg:memory, orientation, language
- Develops over a short period of time
- Caused by the direct physiological consequences of a general medical condition

World Health Organization: ICD - 10

- Impairment of consciousness or attention
- Global disturbance of cognition
- Psychomotor disturbance
- Disturbance of the sleep-wake cycle
- Emotional disturbances

Essential Diagnostic Criteria

- Acute or subacute onset
- Fluctuating course
- Disordered attention and cognition
- Disturbance of psychomotor behavior
  - Agitation, somnulence, hallucinations, paranoia

Clinical Subtypes

- Hyperactive
  - Confusion, agitation, hallucinations, myoclonus
- Hypoactive
  - Confusion, somnulence, withdrawn
  - More likely to be under-diagnosed
- Mixed

Differentiating Delirium from Dementia

Features	Delirium	Dementia
Onset	Acute	Insidious
Course	Fluctuating	Progressive
Duration	Days to weeks	Months to years
Consciousness	Altered	Clear
Attention	Impaired	Normal except in severe dementia
Psychomotor changes	Increased or decreased	Often normal
Reversibility	Usually	Rarely

Symptoms in End Stage Dementia

Symptoms reported last year of person's life who die with dementia:

- Agitation 87%
- Confusion 83%

J. Geriatric Psychiatry 1997

Recognizing and naming delirium is the first step in its appropriate management

Delirium

Why is it important?

Delirium is Common

- Up to 80% of people experience delirium during the final week of life
- 15 – 20% hospitalized cancer patients experience some delirium

Patient Impact

- Greater than > 70 % of seriously ill patients rate mental awareness as important
  - JAMA 2000; 284: 2476 - 2482
- 89% of seriously ill patients would not choose a treatment if the outcome is cognitive impairment; the more risk the less inclined to treatment
  - NEJM 2002; 346: 1061 - 1090

Caregiver Impact

76% witnessed delirium or confusion

38% witnessed these symptoms daily

- Sense of fear and helplessness
- May contribute to caregiver risk for Major Depressive Disorder and quality of life impairments (in aggregate with prevalence and frequency of other distressing events)

Am J Geriatr Psychiatry 2003; 11: 309 - 319

Consequences of Delirium

- Causes a person to be frightened, agitated, and upset
- Interferes with the assessment and treatment of other symptoms
- Increased caregiver burden
- Increases the use of restraints
- Interferes with meaningful communication and interaction

Delirium

What causes it?

Q: Which of the following medications can cause delirium?

1. **Lorazepam**
2. **Hyoscyamine**
3. **Dexamethasone**
4. **All of the above**
5. **None of the above**

Q: Delirium is reversible in what percentage of cases?

1. **~50%**
2. **~25%**
3. **~10%**
4. **~1%**

Case: Paul

- 72 yo man with Alzheimer's disease, lung cancer
- Retired dentist; very active and "in charge" during his life
- Very agitated, combative, trying to get out of bed

Pathophysiology

Inouye SK. N Engl J Med 2006;354:1157-65

- Poorly understood
- Acetylcholine deficiency
- Dopamine excess
- Cytokines
  - Increase blood-brain barrier permeability & alter neurotransmission
- Chronic stress
  - Activates sympathetic nervous system, hypothalamic-pituitary-adrenocortical axis

Which patients are at risk?

Characteristics
- age > 65
- male sex

Cognitive status
- dementia
- cognitive impairment
- depression
- previous delirium

Functional status
- immobility, low activity
- history of falls

Sensory impairment
- visual or hearing impairment

Patients at risk...

Decreased oral intake
- dehydration
- malnutrition

Drugs
- psychoactive drugs
- polypharmacy
- alcohol abuse

Coexisting conditions
- terminal illness
- multiple comorbidities
- chronic renal, hepatic dx
- CVA, neurologic disease
- metabolic derangements
- fracture or trauma

What causes delirium?

Medication side effect **(most common!)**
- Opioids
- Corticosteroids
- Benzodiazepines
- Scopolamine
- Hydroxyzine
- Diphenhydramine
- Hyoscyamine
- Tricyclic antidepressants
- H2 blockers
- NSAIDs
- Metoclopramide
- Alcohol/drug withdrawl

Causes...

- Medical contributors
  - Infection
  - Brain metastates
  - Hepatic encepalopathy
  - Renal failure
  - Hypercalcemia
  - Hyponatremia
  - Hypoxemia
  - Volume depletion
  - Immobilization
  - Pain
  - **Urinary retention**
  - **Constipation**
- Psychosocial contributors
  - Depression
  - Vision/hearing impairment
  - Emotional, spiritual distress
  - Unfamiliar environment

Paul: is he at risk of delirium?

- Predisposing conditions:
  - Dementia
  - Elderly man
  - Metastatic lung cancer
  - Immobility
  - Poor oral intake
  - Polypharmacy
- Possible precipitating factors:
  - Drug side effect?
  - Hypoxemia?
  - Infection?
  - Constipation?
  - Urinary retention?
  - Metabolic disorder?
  - Brain metastates?
  - Emotional distress?

Assessment: history

- Hospice diagnosis, co-morbidities
- Onset of mental status change
- Oral intake, urine output, bowel movements
- Recent medication history

History..

- Review of systems: fever, N/V, pain, dyspnea, cough, edema, decubiti
- Alcohol or illicit drug use
- Falls, safety
- Emotional, spiritual distress

Paul: history

- Metastatic non-small cell lung cancer
- Severe Alzheimer's disease
- More restless, combative in last 3 days
- Hand-fed small, pureed meals & thickened liquids but minimal in 3 days
- Small amount dark urine, no BM in 1 week

Paul...

- Increasing doses of lorazepam in last 1-2 weeks for sleep, anxiety
- Per family, no signs of pain, cough, respiratory distress, edema or falls
- Stage II decubitus on coccyx
- Family very outgoing, emotional; holding vigil at bedside → distressed b/c Paul "pushes us away"

Assessment tools

Casarett DJ, Inouye SK. Ann Intern Med 2001;135:32-40

- Confusion Assessment Method (CAM)
  - 94-100% sensitive, 90-95% specific
  - 10-15 minutes by trained interviewer
- Delirium Symptom Interview
  - 90% sensitive, 80% specific
  - >=15 minutes by trained interviewer

Assessment tools...

- Delirium Rating Scale
  - Based on lengthy interview by psychiatrist
- Memorial Delirium Assessment Scale
  - 82% sensitive, 75% specific
  - >=10 minutes by experienced mental health clinician; designed to rate severity, not screening or diagnosis.

Confusion Assessment Method

- **Feature 1: Acute onset and fluctuating course**
- **Feature 2: Inattention**
- **Feature 3: Disorganized thinking**
- **Feature 4: Altered level of consciousness**

*** The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.**

Assessment: physical exam

- Careful, gentle approach to patient
- Appearance, vital signs
- Focused exam based on history
- Consider rectal exam, catheter

Paul: exam

- Lethargic, frail, elderly man lying in hospital bed; fidgeting of arms, legs; slow but persistent attempts to sit up or slide between siderails; quiet but anxious expression
- CAM: all features present

Paul...

- Afebrile, BP 105/62, HR 95, RR 24
- Positive findings: MM dry; abd distended but soft, quiet BS; rectal +stool; bladder catheter w/cloudy, dark urine; decubitus stable w/o infection

Next steps...

- What are the goals of care?
- What is the patient's prognosis?
- Are the patient and caregivers safe?
- Does the patient appear in distress?
- How is the family coping with the current situation?

Next steps...

- What are the benefits and burdens of:
  - Labs, tests to search for reversible causes of delirium?
    - CBC, lytes, BUN/creat, calcium, glucose, UA, O2 sat
  - Treatments of underlying cause(s)?
    - Antibiotics, oxygen, bladder catheter, other
  - Treatments of agitated behavior?
    - Antipsychotics, sedative hypnotics
    - Change in setting of care

Follow-up: Paul

- Goals of care: peaceful death at home, no hospitalizations, no needlesticks
- disimpacted & started daily laxative regimen
- diagnosed UTI & treated w/ liquid Abx
- weaned lorazepam from 2 mg SL q4 hrs prn to 0.25 mg SL q8 hrs prn

Follow-up (con't)

- started haloperidol 0.5-1 mg SL qHS and q8 hrs prn
- created a calmer environment
- allowed Paul to express/use his energy safely
- in 2-3 days, Paul back to his baseline

Prevention

Best treatment for delirium is to prevent it in the first place!

- Delirium can be reversible in ~50% of episodes (Lawlor et al. Arch Intern Med 2000;160:786-94)
  - Medication-induced, dehydration
- Targeted interventions can prevent delirium in hospitalized older adults (Inouye et al. NEJM 1999;340:669-76)
  - Sleep hygiene, scheduled physical & mental activities, correction of visual & hearing problems, hydration

How do you manage the patient with delirium near the end of life?

What is your first line medical treatment choice for agitated delirium?

1. Haloperidol
2. Chlorpromazine
3. Lorazepam
4. Olazanpine or Risperidone
5. 1, 2, and 4

Which of the following is an appropriate initial intervention for delirium?

1. Music during turns/personal care
2. Minimize ambient sound (alarms, bells, voice)
3. Aromatherapy such as Lavender or Melissa with bed bath
4. Spiritual interventions such as prayer, ritual, meditation
5. Cognitive behavioral therapy for PTSD
6. Engaging family or familiar people in care
7. All of the above

Prevention & Early Intervention:

- Know the risk factors:
  - Who is most at risk for becoming delirious?
- Develop a prevention/intervention plan of care:
  - Physical Environment
  - Physical Suffering
  - Polypharmacy and physiology
  - Psychosocial interaction
  - Existential

So now what?

- Prevention is too late or did not work...
- Assessment of agitation is completed:
  - Anxiety?
  - Dementia?
  - Pain?
  - Delirium?
- Causes of delirium are suspected, now what?

Delirium is a Palliative Emergency

- Monitor carefully
  - Warrants GIP level of care.
- If patient responds negligibly or partially
  - Reevaluate diagnosis/presumed cause
  - Inquire about adherence to medication
  - Consider dosage adjustment
    - *Titrate before rotate - just like with pain!*
  - Consider a different medication
  - Refer to a specialist
- Remember the family and caregivers!

Treatment of Delirium

- Step 1: Treat underlying causes
- Step 2: Non-pharmacological
- Step 3: Pharmacological
- Address family, caregivers and other psychosocial impacts of delirium

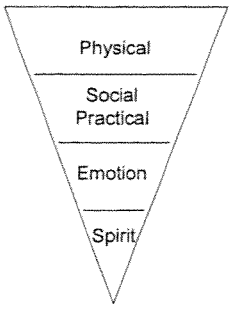
Philip's Struggle

- 63 yo retired photographer with end-stage CHF, in the context of drug abuse history. He was estranged from his family and no longer active in his Jewish faith.
- Severe dyspnea. Now over 2 weeks becoming increasingly confused multiple times each day. Sometimes confusion is agitated, sometimes somnolent.

Step 1: Treat underlying causes

D **D**rugs (Side effects, OD, WD)
E **E**motion (Mania, Anxiety, Depression) Encephalopathy, Environmental change
L **L**ow Oxygen or Hearing/Seeing (Ischemia, CHF, PE, COPD)
I **I**nfection, Intracerebral event or metastasis
R **R**etention (Urine, Feces)
I **I**ntake (Malnutrition, Dehydration), Immobility
U **U**remia
M **M**etabolic (Thyroid, Organ Failure, Electrolytes, Calcium, SAIDH)

Address Physical Causes



- Pain:
  - Does the medicine match the pain?
- Dyspnea:
  - Oxygen - hypoxia can cause delirium
- Constipation/Retention
- Fevers:
  - Pharmacologic
  - Non-pharmacologic: Lemon foot wrap, other cooling techniques
- Others?

Philip's story continued

- "Philip has terminal agitation, and I think he needs more ...?"
  - Is it terminal agitation, or something else?
  - How can you find out?
- Step 1: Treat underlying cause (suspected)

Address Pharmacological Causes:

Remember - First do no harm

Consider stopping, rotating, weaning the following:

- Benzodiazepines (OD/WD/SE)
- Opioids
- Alcohol (OD/WD)
- Anticholinergics
- Anticonvulsants
- Steroids

Questions?

Philip's Medications

- MSContin and Roxinol for dyspnea
- Oxygen
- Lorazepam q4 hours prn for anxiety
- Furosemide qd for edema
- Metoprolol bid for CHF
- Lisinopril for CHF

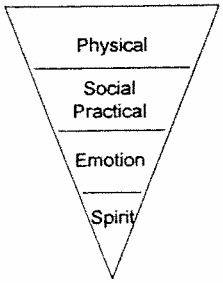
Philip's story continued

- Opioids were rotated.
- Benzos were weaned.
- Assessment for UTI was negative.
- Poor hydration and nutrition status were difficult to reverse.
- Oxygen was increased.
- Chaplain was involved.
  - What happened?

Address Psychosocial Causes

- Post-traumatic stress disorder in veterans.
- Veterans with PTSD who receive a terminal diagnosis often want to:
  - Make sure their story has been heard.
  - Put the traumatic events into some sort of perspective in their lives.
  - Deal with the effects that PTSD has had on their lives, such as mending relationships, giving and accepting closeness and affection, and getting affairs in order.

Address Existential Causes



- Involve the chaplain
- Assess for possible existential crisis or other version of pre-death awareness
- Consider prayer, meditation, mantra, ritual

Mr. U's Existential Suffering

Mr. U's Existential Crisis

- ID: 65 year old retired engineer with metastatic lung cancer to bone.
- HPI: Severe pain, principally in area of leg requiring complex pain management. Now he is experiencing increased confusion, agitation, restlessness at night.
- Past Medical History: Generally healthy until diagnosis.
- Social History: Married to a non-catholic woman. Has 2 grown daughters. Raised Catholic but has not been to church much since his marriage.

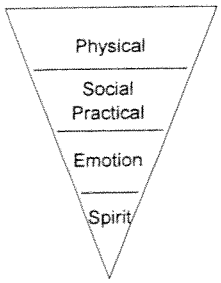
Mr. U's Spiritual Pain

- Fear of the afterlife
- Unresolved regrets
  - sacraments
  - Priest
- Never married in Church
- Importance of ritual
- Importance of witnessing, presencing and non-abandonment, non-judging.

Step 2: Non-Pharmacological Treatments

- Environmental factors
  - Materials (like calendars, clocks) to reorient
  - Adequate soft lighting
  - Identify all individuals
  - Limit number of different individuals
  - Limit stimulation
  - Sitters for safety
  - Engage family, if possible
  - Music therapy

Physical Environment



- Sight:
  - Light/Dark Cycles
  - Visual stimulus/cues
  - Familiar faces
- Sounds:
  - Ambient noise
  - Music therapy
  - Familiar voices
- Smells:
  - Aromatherapy, other?
- Touch

Agitation & Aromatherapy

- Aromatherapy massage RCT showed short-term benefit in anxiety in patients with cancer related anxiety.
- Lavandula augustifolia (Lavender) aromatherapy - agitation in elderly patients with dementia. Cross-over randomized study. N=70
  - Improvement in Agitation ($p<0.0005$), irritability ($p<0.001$), physical aggression, physical behavior non-aggressive, and verbally agitated behavior ($p<0.001$).
  - Other studies showed cutaneous application of oil for effect, given decrease in olfactory function in elderly.

Step 3: Pharmacological Intervention

- What options do we have?
- What is the evidence?

Use of Antipsychotics In Delirium

The Cochrane Collaboration 2005

Review of drug therapy for delirium in terminally ill patients

Multi-database search (1966-2003) for prospective studies w/ or w/o randomization and/or blinding

Of 13 studies only one met criteria:

Breitbart W, et al: A double-blind trial of haloperidol, chlorpromazine and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psych 1996; 153(2): 231-7

Further research essential

Delirium Study

Methods:

- 30 patients consented on admission & q week
- 3 arm blinded study using Lorazepam, Haloperidol or Chlorpromazine
- Doses Doubled At Intervals

Results:

- Haloperidol & Chlorpromazine Effective;
- Lorazepam Worsened Delirium

Breitbart et al. J of Psych 1996

Why Chlorpromazine?

Pharmacological Parameters

Antipsychotic Agent	Chlorpromazine	Haloperidol
Sedation	+++	+
EPS	++	++++
Anticholinergic	++	+
Orthostatic Hypotension	+++	+

++++ = very high incidence, +++ = high incidence, ++ = moderate incidence, + = low incidence

Drug Facts and Comparisons (Oct 2003)

Chlorpromazine (Thorazine): Routes of Administration

- PO:PR:IV/IM = 4:2:1
- PO not recommended; bioavailability ~8%; highly variable
- IV - high peaks cause hypotension
- PR recommended if patient able/willing
- Intermittent SC - irritating
- Continuous SC – w/dexamethasone 2mg

Antipsychotics

	⇩ Sed	⇧ Sed	- EPS
3-7 Days	Haloperidol IM, IV, SC PO (tab/sol) SCI	**Chlorpromazine** IM, IV, PR PO(tab/sol) SCI?	
>7 Days	Risperidone *(Risperdal)* PO (tab,sol,odt) IM (long acting)	Olanzapine *(Zyprexa)* PO (tab,odt) IM (intermittent)	Quetiapine *(Seroquel)* PO (tab) Ziprasidone *(Geodon)* PO (cap) IM (intermittent)

Antipsychotics: Black Box Warning

- The FDA has reported that 5106 elderly patients with dementia treated with atypical (second generation) antipsychotics in 17 randomized controlled trials had a higher mortality rate (4.5% vs. 2.6%) than those receiving placebo.
  - cardiovascular
  - and infectious causes
- What to do about this information?

Philip's Story continues:

Step 3: Add antipsychotic medication

- He began to have fewer hyperactive delirious episodes, but still his mental status waxed and waned.
- Haloperidol was started initially given hypoactive delirium.

Targeted Pharmacological Therapy

- Antipsychotic therapy is first choice.
- Choose based on level of behavior
  - If more hyperactive, consider chlorpromazine
  - If more hypoactive, consider haloperidol
- Titrate medication if initial dose is not effective.
- Consider switching medication if:
  - Lengthy treatment anticipated
  - Lack of response despite increase dose.

If antipsychotics do not work

- Reassess cause - again, depending on goals of care.
- Consider second line option of sedation if needed.
  - This is where recommendations for benzodiazepines, barbiturates or propofol comes into play.
  - This is palliative sedation!

Use of Pharmacotherapy in Delirium

Multi-database search 1966-2002 for "best available evidence"; 14 of 72 met criteria

Recommendations for Terminal Restlessness and Delirium:

	Preferred	Alternative
First Line	Haloperidol	Chlorpromazine
Second Line (sedation as goal)	Midazolam (or other benzo)	Propofol

Kehl K: Treatment of terminal restlessness: A Review of the Evidence, 2004. J Pain & Pal Care Pharm Vol. 18(1) 2004.

Philip's story: conclusion

- Despite aggressive interventions, he awoke with more alertness for a brief period of time.
- Now he showed signs of active dying:
  - Mottling of hands and feet
  - Irregular breathing patterns
- Chlorpromazine suppositories were given.
- He died peacefully 7 days later.

Terminal Delirium

- Diagnosis of exclusion
- Delirium during the dying process
  - Signs of the dying process
- Multiple causes, often irreversible
- Sedating antipsychotics
- Lorazepam or midazolam to settle, back-up option

Summary

- Agitation is a sign, not a diagnosis
- Know the difference: Delirium, Dementia, Anxiety
- If it is delirium, assess possible causes
- Terminal Delirium is a diagnosis of exclusion, should not be presumed.
- Use step-wise approach to treat:
  1. Address the underlying cause
  2. Use non-pharmacological interventions
  3. Use targeted pharmacological interventions
  4. Sedation if need be (non-targeted therapy)

Confusion Assessment Method

Feature 1: Acute Onset and Fluctuating Course	This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2: Inattention	This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3: Disorganized thinking	This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4: Altered Level of consciousness	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

Delirium References

August 2007

Suzana Makowski, MD
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