EPEC-O

Education in **P**alliative and **E**nd-of-life **C**are - **O**ncology

Participant's Handbook

Module 3g:

Symptoms – Delirium

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Case*

A 72-year-old married man with metastatic lung cancer is admitted to a palliative care unit with a two-day history of confusion and aggressive behavior. Over the next two days, he demonstrates intermittent agitation, confusion, and disorientation. These seem to be worst at night, while in mid-morning, he was observed to be deeply asleep. At times he shouts out about patients 'going missing,' and believes that his life is in danger. Staff on the unit are unable to determine any recognizable pattern in his outbursts. His wife reports that in between periods of agitation, he can be cooperative and 'back to his normal self.' His medications include ranitidine, dexamethasone, gabapentin, and lorazepam. He uses opiate analgesics as needed for pain. Examination reveals non-specific neurological abnormalities. His vital signs show mild hypertension, tachycardia, and an elevated respiratory rate. CT scan confirms cerebral metastases. An initial Folstein Mini-Mental State Examination demonstrates problems in orientation, recall, and attention, with a total score of 18 of 30.

* This case is not on an EPEC-O Curriculum trigger tape.

Introduction

Delirium is *both*

- *A disturbance of consciousness* with reduced awareness of the environment and reduced ability to focus, sustain, or shift attention, and
- *A change in cognition* with memory deficits, disorientation, language disturbance, or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.

In contrast to dementia which develops slowly, delirium develops over a short period of time, usually hours to days, and fluctuates during the course of the day.

There may be associated alterations in sleep patterns, eg, day-night reversal, emotional states, non-specific neurological abnormalities and a sudden and significant decline in functional ability.[1]

While delirium presents with psychiatric symptoms, it is important to remember that these symptoms are manifestations of medical abnormalities and not primary psychiatric illness.

In a cancer patient, it is particularly important to be vigilant about delirium postoperatively, after chemotherapy treatment, when infections are present, with tumor necrosis, and in advancing illness. Older patients are particularly susceptible and recover slowly. Mortality rates are high and symptoms can be very distressing for patients and extraordinarily difficult on their families and caregivers.

Delirium can have different clinical presentations or sub-types. The 'hyperactive' subtype is most often recognized due to its associated behavioral disturbances, and the frequent

occurrence of psychotic symptoms such as hallucinations or delusional beliefs. The 'hypoactive' subtype, or quietly delirious patient, is often mistaken for depression or fatigue. Not infrequently, patients will present with a 'mixed' subtype with symptoms of both 'hyper' and 'hypo' active subtypes over the course of a day. Often it is the waxing and waning nature and time course of onset that points to the diagnosis of delirium. Once the diagnosis of delirium is suspected, the underlying cause of the disturbance can be investigated.[1,2]

Prevalence

Delirium is a common, yet underrecognized and undertreated, medical condition. It has been reported in up to 80-85% of terminally ill patients.[1,3]

Prognosis

Delirium is associated with an increased risk of complications, protracted hospitalizations, and postoperative recovery.[4,5] Up to 25% of delirious patients die within six months.[6]

Delirious elderly patients are at particular risk for complications such as pneumonia, skin ulceration and falls.[7] In elderly, the risk of dying during a hospital admission increases to between 22-76%.[8,9]

Pathophysiology

There are many possible causes of delirium.[10] Table 1 presents the most important and potentially life threatening causes and integrates a mnemonic 'I WATCH DEATH.' Those most commonly seen in patients with advanced cancer are italicized. [11,12]

In cancer patients, be particularly vigilant about delirium caused by infection, metabolic imbalances, medications and tumor necrosis. In addition, infections, such as pneumonia or a urinary tract infection can be enough to cause a delirium in older patients.

Table 1: Causes of delirium

Infection	*Encephalitis, meningitis, syphilis, HIV, sepsis*
Withdrawal	*Alcohol*, barbiturates, *sedative-hypnotics*
Acute metabolic	*Acidosis, alkalosis, electrolyte disturbance, hypercalcemia, hepatic failure, renal failure*
Trauma	Closed head injury, heatstroke, postoperative, severe burns
CNS pathology	*Abscess*, *hemorrhage*, hydrocephalus, *subdural hematoma*, *infection*, *seizures*, *stroke*, *tumors*, *metastases*, vasculitis
Hypoxia	*Anemia*, CO poisoning, hypotension, *pulmonary or cardiac failure*
Deficiencies	Vitamin B12, folate, niacin, thiamine
Endocrinopathies	Hyper/hypoadrenocorticism, *hyper/hypoglycemia*, myxedema, hyperparathyroidism, hypercalcemia
Acute vascular	Hypertensive encephalopathy, stroke, *arrhythmia*, *shock, dehydration*
Toxins or drugs	*Medications, chemotherapeutics, illicit drugs,* pesticides, solvents
Heavy metals	Lead, manganese, mercury

Medications, both prescription and over the counter, are the most common cause of delirium. Anticholinergic medications are often associated with this problem. Table 2 outlines various medication classes and medications frequently associated with delirium.[12,13]

Table 2: Medications causing delirium

Analgesics	Clonidine
Anesthetics	Corticosteroids
Antiasthmatics	Immunosuppressives
Anticholinergics, including medications with anticholinergic properties	Insulin
Anticonvulsants	Gastrointestinals
Antihistamines	Muscle relaxants
Antihypertensives	Phenytoin
Antimicrobials	Psychotropics, especially those with anticholinergic properties
Antiparkinsonian	Ranitidine
Cardiac glycosides	Salicylates
Cimetidine	Sedatives

Neuropathophysiology

Several cortical and subcortical areas seem to be affected by delirium. Three areas of the prefrontal cortex appear to be involved in certain presentations of delirium. The dorsolateral prefrontal cortex has been associated with executive cognition. Damage to the orbitomedial prefrontal cortex can result in a disinhibition. Abnormalities in the function of the anterior cingulate gyrus may account for the lack of language or perseveration sometimes seen in delirious patients. The parietal cortex has also been shown to be affected by delirium. The third major area of the brain affected by delirium is the thalamus and caudate. Its connections with the reticular activating system accounts for the changes in level of consciousness of patients with delirium.

Neurotransmitter changes in the areas noted above have also been implicated in the development of delirium. There are several neurotransmitters involved, including acetylcholine, dopamine, serotonin, GABA, norepinephrine, glutamine, and histamine. Reduced acetylcholine, either through pathologic processes or anticholinergic medications, is a very common cause of delirium.

Higher cognitive and executive functions associated with this area of the brain must remain intact for normal behavior, cognition, and planning.

A recent study demonstrated reduced regional cerebral perfusion during periods of delirium in comparison to studies after recovery.[14]

Assessment

To assess for delirium, take a careful history, perform a physical examination, carefully observe the patient's ability to maintain attention over time, and order appropriate investigations (see Table 2).[11,12,15,2]

The Folstein Mini-Mental State examination is a screening tool to assess cognitive impairment. Serial administration of the tool can aide in the assessment of delirium and the response to treatment (see Appendix I).[16] Several other tools have been developed to assess delirium, including the Confusion Assessment Method (CAM, a diagnostic tool),[17] Delirium Rating Scale (DRS, a diagnostic tool),[18] Saskatoon Delirium Checklist (SDC),[19] and Memorial Delirium Assessment Scale (MDAS, validated as both a screening tool and a severity rating scale).[20] These tools are more likely to be used by psychiatrist or palliative medicine physicians who are experts in delirium assessment and management.

While laboratory investigations are not specific or sensitive enough to make a definitive diagnosis of delirium, they can help to determine the underlying cause. An electroencephalogram will usually show generalized slowing, but in the case of delirium due to alcohol withdrawal, it can show low voltage fast activity.[21,22]

Table 2: Assessment of delirium

Physical status	Mental status	Basic laboratory	Additional investigations
History Physical and neurological exam Review of vital signs Review of medical records Review of medications	Interview Cognitive tests Clock face drawing Trail A&B Folstein mini-mental state examination	Electrolytes Glucose Calcium Albumin Blood urea nitrogen Creatinine SGOT Bilirubin Alkaline phosphatase Magnesium Phosphate VDRL CBC Serum drug levels Arterial blood gas Urinalysis and culture Urine drug screen Electrocardiogram Chest X-ray B12, folate TSH	EEG Lumbar puncture CT or MRI brain Heavy metal screen Antinuclear antibody Urinary porphyrins HIV testing

Delirium vs. dementia

It is often necessary to differentiate delirium from dementia.[15]

Table 3: Differences between delirium and dementia

	Delirium	Dementia
Change in alertness Disturbance of consciousness	Yes	No
Temporal profile of symptoms: Onset	Usually develop quickly, over hours to days	Gradual onset
Fluctuate over a 24-hour period	Yes	No

While memory impairment is common to both, dementia is not associated with a change in alertness or any disturbance in consciousness. The temporal profile is also different. In delirium, symptoms usually develop over hours to days and often fluctuate over a 24-hour period. In dementia, symptoms typically develop much more gradual and there is little or no variation of symptoms over time.

Management

The management of delirium is multifaceted and multidisciplinary. Interventions to treat the underlying causes, and ameliorate the troublesome symptoms are of utmost importance. Ensure adequate hydration without creating peripheral or pulmonary edema.

As medications are frequently implicated, decrease or discontinue any unnecessary medications, particularly those with anticholinergic properties. Some analgesics, eg, meperidine or pentazocine, are strongly anticholinergic, have a high risk of adverse effects, eg, CNS excitation, and will need to be replaced by other analgesics. Medications may accumulate secondary to half life, hydration status, changes in renal clearance, or liver function abnormalities. As opioid clearance is dependent on renal function, reduce the routine opioid dose by at least 50% when urine output is < 500 ml/24 hr, and stop routine dosing when urine output is < 200 ml/24 hr.

Other reversible causes of delirium that can be quickly determined and treated are hypoglycemia, hypoxia or anoxia, hyperthermia, substance or medication withdrawal, and anticholinergic delirium. For difficult-to-manage delirium, consult a psychiatrist for assistance.

Non-pharmacological management

A hyperactive delirium can be quite distressing to the observer. Help family understand that what the patient is experiencing might be quite different from what the family is observing.

A number of environmental factors are important when treating delirious patients:[23]

- Communicate clearly and concisely with the patient.
- Include frequent reminders of the date and time.
- Always identity important individuals.
- Minimize the number of different staff working with the patient.
- Provide materials to help reorient the patient, eg, a clock, calendar, and schedule of daily activities.
- Encourage the family and caregivers to bring in familiar objects from home.
- To minimize excess noise and ensure optimal stimulation by nursing staff, move delirious patients to single rooms, close to the nursing station.
- Minimum excess noise; control other environmental factors, eg, temperature and lighting.
- Avoid understimulation. As sensory impairments can make this worse, provide needed glasses and hearing aids.

- If patients are restless, provide sitters to calm and reorient them. Only use physical restraints if there is a high risk of harm to the patient or staff.

Pharmacological management

Patients with delirium often require antipsychotics and occasionally benzodiazepines. While is some question about how to treat delirium depending on the goals of care, the type of delirium (hyperactive, hypoactive, or mixed), or whether the etiology is thought to be reversible or irreversible, there may be advantages to treating delirium consistently, regardless of type or etiology.[24]

Antipsychotic medications

Antipsychotics are the medications of choice to treat delirium. Depending on the goals of care, those that are non-sedating may be preferred over those that tend to be sedating.

Both haloperidol and chlorpromazine have been shown to be superior to lorazepam for the treatment of delirium.[25] Since its development, haloperidol has been the gold-standard pharmacotherapy.[10] Its use is safe in medically ill patients and it is not sedating. It is available in oral, intramuscular, and intravenous formulations. Common starting doses are:

- Haloperidol (non-sedating), 1-2 mg PO, IM, IV q 2–4 h (0.25–0.5 mg q 4 h in the elderly). Titrate to effect. There is a wide dosage range. Doses of 0.5–20 mg IV have been used with success. There are reports of hundreds of milligrams being given over the course of a day with few ill effects.

The need for sedation within the context of agitated behavior is not uncommon. In patients where the use of concomitant benzodiazepine is undesirable, it may be beneficial to consider a low potency antipsychotic medication such as chlorpromazine, to achieve symptomatic control of agitation. Use it cautiously as it is relatively anticholinergic and can contribute to the delirium.[26]

- Chlorpromazine (sedating), 10-25 mg PO, PR, IM, IV q 6 h. Titrate to effect.

In the mid to late 1990s a new class of antipsychotic medication came into use. These "novel neuroleptics" have a different mechanism of action. Instead of primarily blocking dopamine receptors, as with the older antipsychotics, these new medications act through serotonin receptors in addition to or over dopamine receptors. More data is accumulating about the use of the newer atypical antipsychotics, including risperidone, olanzapine, and quetiapine.[27,28] These agents may offer an advantage over haloperidol by means of a lower incidence of extrapyramidal side effects. They have been used in the treatment of delirium as shown by previously published case reports and case series.[27,29,30] Well-controlled, blinded studies of the atypical antipsychotics in the treatment of delirium have yet to be completed. Common starting doses are:

- Risperidone (non-sedating), 0.5–1 mg PO q 12-24 h

- Olanzapine (sedating), 2.5–5 mg PO q 12-24 h
- Quetiapine (sedating), 100 mg PO nightly. Titrate to effect. Typical dose is 300–400 mg PO nightly.

Day-night reversal

If there is a sleep cycle disturbance, the use of more sedating antipsychotics, eg, chlorpromazine, olanzapine, or quetiapine, may be more helpful. Common starting doses are:

- Chlorpromazine (sedating), 10 mg PO nightly. Increase by 10 mg PO nightly to 30–50 mg PO nightly.
- Olanzapine (sedating), 2.5–5 mg PO nightly. Titrate to effect. Typical dose is 5–10 mg PO daily.
- Quetiapine (sedating), 100 mg PO nightly. Titrate to effect. Typical dose is 300–400 mg PO nightly.

Managing adverse effects

Adverse effects of antipsychotics include extrapyramidal effects, tardive dyskinesia, neuroleptic malignant syndrome, akathisia, lowering of the seizure threshold, and QTc prolongation, ie, > 450 msec or > 25% of baseline EKGs. All of these side effects may lessen with a decreased dose. Akathisia can be managed with a beta-blocker or benzodiazepine.

Extrapyramidal effects can be managed with anticholinergic medications such as benztropine or diphenhydramine.

Note: Anticholinergic medications and benzodiazepines are generally contraindicated in delirium. Try decreasing the dose of the antipsychotic or try another antipsychotic. This may be the best choice.

For dystonic reactions, eg, oculogyric crisis, dysphagia, torticollis (cervical muscle spasm producing unnatural twisting of the head), or opisthotonos, (a tetanic spasm with head and heels bent backward, body bowed forward):

- Diphenhydramine, 25–50 mg PO, IM, IV q 4 h PRN and consult a psychiatrist urgently

For akathisia (a sense of constant motor restlessness)

- Benztropine, 1–2 mg PO daily–bid

For parkinsonian reactions (tremor, bradykinesia, rigidity, abnormalities of gait and posture):

- Benztropine, 1–2 mg IV, IM acutely. Then 1–2 mg PO daily–bid.

For tardive dyskinesia (involuntary movements of lips, tongue, jaws, extremities) caused by dopaminergic drugs, eg, haloperidol, that persists after medication is stopped consult psychiatry.

Benzodiazepines

If the delirium is secondary to specific states, eg, alcohol withdrawal, a benzodiazepine taper would be the appropriate treatment. Consult a psychiatrist if you are unsure how to appropriately treat alcohol withdrawal.

For all other causes of reversible delirium, avoid benzodiazepines as first line therapy. They are more likely to cause further disinhibition rather than sedation in this state and in geriatric populations.[31]

However, low dose lorazepam used in conjunction with antipsychotic medication may offer additional benefits when antipsychotic medication alone has not been sufficiently effective, and some studies suggest there may be a synergistic effect that allows for increased effectiveness with decreased adverse effects.[32]

Side effects of benzodiazepines include sedation, behavior disinhibition, amnesia, ataxia, respiratory depression, dependence, and delirium. Special attention must be given to the accumulation of benzodiazepines with longer half-lives (such as diazepam and clonazepam).

Terminal delirium

Terminal delirium is *delirium that occurs during the dying process*. It is always associated with other signs of the dying process, eg, decreased level of consciousness, changes in breathing patterns, loss of ability to swallow, peripheral cooling, venous pooling/mottling, oliguria or anuria (see EPEC-O Module 6: Last Hours of Living).

Unlike the delirium that occurs earlier in an illness, once a patient is actively dying, end-organ failure, hypoxia, infections, medication toxicity, eg, opioids, metabolic disturbances can all contribute to neuronal compromise and/or death and a picture of delirium that is irreversible.[24,33,34]

In addition to a decrease in alertness, terminal delirium typical manifests as restlessness, confusion, tremulousness, hallucinations, mumbling, moaning/groaning associated with day-night reversal and decreasing level of consciousness. If unmanaged, it can evolve to include myoclonic jerks and seizures. It can also be very distress for everyone who watches.

As the delirium and the dying process are irreversible, the focus of treatment changes from reversing the underlying cause to settling the patient and educating and calming the family. Most dying patients prefer to be sedated, relaxed, and have no memory of the event. Benzodiazepines are ideal for this role as they are anxiolytic/hypnotics, muscle relaxants, amnestics, and antiepileptics. Common starting doses are:

- Lorazepam 1.0–2.0 mg predissoved in 3-5 ml water, place against oral or buccal mucosa q 1 h PRN. Once the pain has settled, calculate the total amount of medication that was used in the last 24 hours, then dose routinely and offer a breakthough sedative at the beside.

There is some literature regarding the use of continuous infusion of intravenous benzodiazepine for sedation for terminal delirium.[3,35] In these cases, midazolam has been used as it has a very rapid onset of action and a short half-life.

Summary

Delirium is an important clinical entity to recognize, diagnose, and treat in patients receiving end of life care. There is still much to learn about predictors of delirium, subtypes of delirium, and symptomatic treatment of this condition. Effective treatment of delirium will decrease the suffering of the patient and their families. Restoring a patient's ability to attend to his or her surroundings and environment decreases suffering, and facilitates communication with the treatment team and family. This ultimately allows for a better quality of life and death.

Key take-home points

1. Delirium is common among the seriously ill.
2. Delirium causes suffering and is associated with increased morbidity and mortality.
3. Treat underlying condition.
4. Manage with neuroleptics, anxiolytics as adjuncts.

Pearls

1. Be alert to harbingers: day-night reversal, new emotional states, sudden neurological decline.
2. Explain to the family that behaviors associated with delirium do not reflect his or her personality or relational meaning.

Pitfall

1. Lack of knowledge about terminal delirium is common. Memories of it among surviving family members can be traumatic. Be part of the solution. Learn to recognize and manage early.

Appendix: Folstein Mini-Mental Status Examination

Use the Folstein Mini-Mental Status tool routinely to assess for cognitive impairment. A totalled score of >24 is normal. 15-24 indicates mild to moderate impairment; < 15 indicates significant impairment.

Maximum Score	Score	
5	_____	What is the (year) (day) (month) (date) (season)?
5	_____	Where are we (province) (country) (town) (hospital) (floor)?
3	_____	Name 3 objects Glass, Blanket, Pencil
5	_____	Serial 7's or Alternately spell "world" backwards
3	_____	Ask for the 3 objects repeated above
2	_____	Name a pencil and watch
1	_____	Repeat the following – "no ifs, ands or buts"
3	_____	Follow a 3-stage command: "t*ake a paper in your right hand, fold it in half and give it to me*"
1	_____	Read and obey the following: *Close Your Eyes*
1	_____	Write a sentence
1	_____	Copy a design
30	_____	TOTAL SCORE

References

[1] Practice guideline for the treatment of patients with delirium. American Psychiatric Association. *Am J Psychiatry*. 1999;156(5 Suppl):1-20. PMID: 10327941.

[2] Lipowski ZJ. Delirium (acute confusional states). JAMA. Oct 2 1987;258(13):1789-1792. PMID: 3625989.

Delirium, can occur at any age, but elderly persons are especially prone to develop it. In later life, it is often a conspicuous feature of systemic or cerebral disease and drug (notably anticholinergic) toxicity, and it may constitute a grave prognostic sign. Its development in a hospitalized patient may interfere with his or her management, disrupt ward routine, and cause medicolegal complications as a result of patient injury. Acute onset of a fluctuating level of awareness, accompanied by sleep-wake cycle disruption, lethargy or agitation, and nocturnal worsening of symptoms, are diagnostic. Early recognition of delirium and treatment of its underlying cause are essential.

[3] Breitbart W, Strout D. Delirium in the terminally ill. *Clin Geriatr Med*. 2000;16(2):357-372. PMID: 10783433.

Delirium is highly prevalent in terminally ill patients, especially in the last weeks of life, when some cognitive impairment develops in as many as 85% of patients. Delirium is associated with increased morbidity in terminally ill patients and can interfere with pain and symptom control. The cause of

delirium is usually multifactorial and often cannot be found or reversed in dying patients. Nonpharmacologic and pharmacologic interventions are effective in controlling the symptoms of delirium in terminally ill patients. Haloperidol and other newer neuroleptics are safe and effective in eliminating delirium for some patients. In approximately one third of patients, delirium can be managed successfully only by providing sedation.

[4] Stevens LE, de Moore GM, Simpson JM. Delirium in hospital: does it increase length of stay? *Aust N Z J Psychiatry*. 1998;32(6):805-808. PMID: 10084344.

To determine the effect of delirium, as a comorbid diagnosis in hospitalised patients, on patient length of stay. Delirious patient length of stay was found to be significantly longer (2.2-fold; 95% confidence interval 1.5-3.3) than matched controls. Delirium, as a comorbid diagnosis in general hospital patients, is associated with an increased use of resources. Its early diagnosis may limit this and morbidity.

[5] Franco K, Litaker D, Locala J, Bronson D. The cost of delirium in the surgical patient. *Psychosomatics*. 2001;42(1):68-73. PMID: 11161124.

The authors identified the added cost attributable to postoperative delirium in patients undergoing elective surgery. Patients (n = 500) were evaluated before elective surgery, assessing cognitive functioning, medical conditions, medication usage, and other information regarding their health status. Using DSM-IV criteria, patients were assessed for delirium on postoperative days 1-4. Of the 500 patients assessed, 57 (11.4%) developed delirium during the study.

[6] Trzepacz PT, Teague GB, Lipowski ZJ. Delirium and other organic mental disorders in a general hospital. *Gen Hosp Psychiatry*. 1985;7(2):101-106. PMID: 3996899.

133 cases of organic mental disorders from a total of 771 patients who were referred for psychiatric consultation from a general hospital were analyzed. Delirium and dementia are most commonly diagnosed and features of these, particularly in the geriatric population, are described. Delirium was more frequent in patients with multiple medical problems, was an indicator of poor prognosis having the highest mortality rate, and was usually undiagnosed by the referring physician.

[7] O'Keeffe ST, Lavan JN. Clinical significance of delirium subtypes in older people. *Age and Ageing*. 1999;28(2):115-119. PMID: 10350406. Full Text

Examination the relative frequency and outcome of clinical subtypes of delirium in 94 older hospital patients with delirium from a prospective study of 225 admissions. Also examined were illness severity on admission, prior cognitive impairment, mortality, duration of hospital stay and hospital-acquired complications. Of the 94 patients, 20 (21%) had a hyperactive delirium, 27 (29%) had a hypoactive delirium, 40 (43%) had a mixed hypoactive-hyperactive psychomotor pattern and seven (7%) had no psychomotor disturbance. There were significant differences between the four groups in illness severity ($P < 0.05$), length of hospital stay ($P < 0.005$) and frequency of falls ($P < 0.05$). Patients with hypoactive delirium were sicker on admission, had the longest hospital stay and were most likely to develop pressure sores. Patients with hyperactive delirium were most likely to fall in hospital.

[8] Rabins PV, Folstein MF. Delirium and dementia: diagnostic criteria and fatality rates. *Br J Psychiatry*. 1982;140:149-153. PMID: 7074297.

Medically ill patients diagnosed at index admission as delirious, i.e., suffering cognitive decline and an altered state of consciousness, had higher fatality rates than demented, cognitively intact or depressed patients. At a one-year follow-up the death rate of those who had been delirious was still higher than that of demented patients. Delirious patients were more likely to have a diffusely slow EEG, tachycardia and hyperthermia and lower mean systolic and diastolic blood pressure.

[9] Flint FJ, Richards SM. Organic basis of confusional states in the elderly. *Br Med J*. 1956;44(5008):1537-1539. PMID: 13374375.

[10] Trzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. *Psychiatr Clin North Am*. 1996;19(3):429-448. PMID: 8856810.

This article discusses research in the areas of morbidity and mortality, epidemiologic risk factors, phenomenology, pathophysiology, and treatment of delirium. Delirium assessment instruments are reviewed. The neuropathophysiologic understanding of delirium is discussed in the context of important CNS neural circuitry. Pharmacologic treatments of delirium in adults and children are outlined.

[11] Rundell JR, Wise MG, Press AP. Essentials of consultation-liaison psychiatry : based on the *American Psychiatric Press textbook of consultation-liaison psychiatry*. 1st ed. Washington, DC: American Psychiatric Press; 1999.

[12] Practice guideline for the treatment of patients with delirium. American Psychiatric Association. *Am J Psychiatry*. 1999;156(5 Suppl):1-20. PMID: 10327941.

[13] Kaplan HI, Sadock BJ. *Kaplan and Sadock's synopsis of psychiatry : behavioral sciences, clinical psychiatry*. 8th ed. Baltimore: Williams & Wilkins; 1998.

[14] Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. *Psychiatry Clin Neurosci*. 2003;57(3):337-339. PMID: 12753576.

A possible mechanism of delirium was examined by using xenon-enhanced computed tomography to measure the regional cerebral blood flow (rCBF) of the patients both during delirium and after improvement from delirium. Findings that reduced rCBF during delirium becomes normal once delirium improves suggest that a possible cause of delirium may be the cerebral hypoperfusion.

[15] *Diagnostic and statistical manual of mental disorders. 4th, text revision ed*. Washington, DC. American Psychiatric Association; 2000.

[16] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. PMID: 1202204.

[17] Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948. PMID: 2240918.

A new standardized confusion assessment method (CAM) that enables nonpsychiatric clinicians to detect delirium quickly in high-risk settings developed and validated. The study included 56 subjects, ranging in age from 65 to 98 years. The CAM instrument, which can be completed in less than 5 minutes, consists of nine operationalized criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). An a priori hypothesis was established for the diagnostic value of four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM algorithm for diagnosis of delirium required the presence of both the first and the second criteria and of either the third or the fourth criterion. The CAM algorithm had the highest predictive accuracy for all possible combinations of the nine features of delirium, and is sensitive, specific, reliable, and easy to use for identification of delirium.

[18] Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Res*. 1988;23(1):89-97. PMID: 3363018.

A 10-item clinician-rated symptom rating scale for delirium is presented. As compared to demented, schizophrenic, and normal control groups, 20 delirious subjects scored significantly higher on the scale, which quantitates multiple parameters affected by delirium. The scale can be used alone or in conjunction with an electroencephalogram and bedside cognitive tests to assess the delirious subject.

[19] Miller PS, Richardson JS, Jyu CA, Lemay JS, Hiscock M, Keegan DL. Association of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. *Am J Psychiatry*. 1988;145(3):342-345. PMID: 3344848.

Low-dose scopolamine, given as presurgery medication, resulted in low levels of serum anticholinergic activity and caused measurable cognitive impairment in 18 psychiatrically healthy elderly patients. The degree of impairment was directly related to serum anticholinergic activity levels and, in the small subgroup of patients scheduled for spinal anesthesia, to CSF anticholinergic activity. Two of the mental status tests used, the Rey Auditory-Verbal Learning Test and the Saskatoon Delirium Checklist, were sensitive enough to detect these mild drug-induced changes, while two other tests, the Mini-Mental State and the Symbol Digit Modalities Test, were not.

[20] Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage*. 1997;13(3):128-137. PMID: 9114631.

Two studies were conducted in medically hospitalized cancer and acquired immunodeficiency syndrome (AIDS) patients to assess the reliability and validity of a new measure of delirium severity, the Memorial Delirium Assessment Scale (MDAS). Results indicated high levels of inter-rater reliability for the MDAS and the individual MDAS items, as well as high levels of internal consistency. Mean MDAS ratings differed significantly between delirious patients and the comparison sample of patients with other cognitive impairment disorders or no cognitive impairment. The second study compared MDAS ratings of 51 medically hospitalized delirious patients with cancer and AIDS made by one clinician to ratings on several other measures of delirium (Delirium Rating Scale, clinician's ratings of delirium severely) and cognitive functioning (Mini-Mental State Examination) made by a second clinician. Results demonstrated a high correlation between MDAS scores and ratings on the Delirium Rating Scale, the Mini-Mental State Examination, and clinician's global ratings of delirium severity. The findings indicate that the MDAS is a brief, reliable tool for assessing delirium severity among medically ill populations that can be reliably scored by multiple raters. The MDAS is highly correlated with existing measures of delirium and cognitive impairment, yet offers several advantages over these instruments for repeated assessments which are often necessary in clinical research.

[21] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. 1959. *J Neuropsychiatry Clin Neurosci*. 2004;16(4):526-538. PMID: 15616182.

[22] Pro JD, Wells CE. The use of the electroencephalogram in the diagnosis of delirium. *Dis Nerv Syst*. 1977;38(10):804-808. PMID: 908245.

[23] Meagher DJ. Delirium: optimizing management. *BMJ*. 2001;322(7279):144-149. PMID: 11153573.

[24] Breitbart W, Cohen K. Delirium in the Terminally Ill. In: Chochinov HM, Breitbart W, eds. *Handbook of psychiatry in palliative medicine*. New York: Oxford University Press; 2000:435.

[25] Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry*. 1996;153(2):231-237. PMID: 8561204.

The efficacy and side effects of haloperidol, chlorpromazine, and lorazepam for the treatment of the symptoms of delirium in adult AIDS patients was examined with a randomized, double-blind,

comparison trial. 244 non-delirious, medically hospitalized AIDS patients were monitored prospectively for the development of delirium. Patients entered the treatment phase of the study if they met DSM-III-R criteria for delirium and scored 13 or greater on the Delirium Rating Scale. Efficacy and side effects associated with the treatment were measured with repeated assessments using the Delirium Rating Scale, the Mini-Mental State, and the Extrapyramidal Symptom Rating Scale. Treatment with either haloperidol or chlorpromazine in relatively low doses resulted in significant improvement in the symptoms of delirium as measured by the Delirium Rating Scale. No improvement in the symptoms of delirium was found in the lorazepam group. Cognitive function, as measured by the Mini-Mental State, improved significantly from baseline to day 2 for patients receiving chlorpromazine. Treatment with haloperidol or chlorpromazine was associated with an extremely low prevalence of extrapyramidal side effects. All patients receiving lorazepam, however, developed treatment-limiting adverse effects. Although only a small number of patients had been treated with lorazepam, the authors became sufficiently concerned with the adverse effects to terminate that arm of the protocol early.

[26] Minzenberg MJ, Poole JH, Benton C, Vinogradov S. Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry*. 2004;161(1):116-24. PMID: 14702259. Full Text

In 106 clinically stable patients with schizophrenia. the anticholinergic load was associated with lower scores on measures of attention and declarative memory, including several measures of auditory and visual memory and two tests of complex attention, but was unrelated to intelligence, simple attention, working memory, executive functions, conceptual fluency, or motor speed.

[27] Schwartz TL, Masand PS. The role of atypical antipsychotics in the treatment of delirium. *Psychosomatics*. 2002;43(3):171-174. PMID: 12075031.

Delirium is generally characterized by acute disturbances of consciousness, cognition, and perception that are precipitated by an underlying medical condition. The gold standard of psychiatric treatment is to treat the underlying medical cause and use high-potency antipsychotics to treat the clinical manifestations of delirium. In the early 1990s, a new generation of novel antipsychotics was developed. Their mechanism of action, preferential serotonergic (5HT(2a)) blockade, results in a markedly lower rate of extrapyramidal side effects, an advantage over the typical, older antipsychotic medications. These agents have been shown to be effective and well tolerated in common psychotic disorders (e.g., schizophrenia or bipolar disorder). This paper reviews the pertinent literature and summarizes tentative guidelines for novel antipsychotic use in delirium.

[28] Cook IA. Guidleine watch: Practice guideline for the treatment of patients with delirium. Available at: http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

[29] Horikawa N, Yamazaki T, Miyamoto K, et al. Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. *Gen Hosp Psychiatry*. 2003;25(4):289-292. PMID: 12850662.

Delirium is a common psychiatric illness among medically compromised patients. There is an increasing opportunity to use atypical antipsychotics to treat delirium. A prospective open trial on risperidone was carried out in 10 patients with delirium. At a low dose of 1.7 mg/d, on average, risperidone was effective in 80% of patients, and the effect appeared within a few days. There were no serious adverse effects. However, sleepiness (30%) and mild drug-induced parkinsonism (10%) were observed; the symptom of sleepiness was a reason for not increasing the dose. This trial is a preliminary open study with a small sample size, and further controlled studies will be necessary.

[30] Passik SD, Cooper M. Complicated delirium in a cancer patient successfully treated with olanzapine. *J Pain Symptom Manage*. 1999;17(3):219-223. PMID: 10098365.

Delirium is common among cancer patients, especially those with advanced disease. Typical treatment involves addressing the underlying cause if possible; eliminating nonessential and/or other drugs that can worsen confusion, manipulating the environment; and administering antipsychotic drugs to control symptoms and agitated behavior, and attempt to clear the patient's sensorium. The newer atypical antipsychotics may have potential in the treatment of delirium and also have the added benefit of causing less akathisia and other extrapyramidal side effects. The potential utility of this atypical antipsychotic in the palliative care setting is discussed.

[31] Meagher DJ. Delirium: optimising management. *BMJ*. Jan 20 2001;322(7279):144-149. PMID: 11159573.

[32] Practice guideline for the treatment of patients with delirium. American Psychiatric Association. *Am J Psychiatry*. 1999;156(5 Suppl):1-20. PMID: 10327941.

[33] Ferris FD. Last hours of living. *Clin Geriatr Med*. 2004;20(4):641-667. PMID: 15541617.

The last hours of living can be one of the most important times in the life of any patient and his/her family. With appropriate preparation and careful management of the process by skilled clinicians, dying and death can be a comfortable and even rewarding experience for everyone involved. After death, careful attention to the grief of survivors can help them cope with their loss and rebuild their lives.

[34] Morita T, Tei Y, Inoue S. Agitated terminal delirium and association with partial opioid substitution and hydration. *J Palliat Med*. 2003;6(4):557-563. PMID: 14516497.

Delirium is often a distressing symptom for both patients and their families, and its prevention is important. New strategies to prevent agitated delirium that are practically available should be explored.

[35] Stiefel F, Fainsinger R, Bruera E. Acute confusional states in patients with advanced cancer. *J Pain Symptom Manage*. 1992;7(2):94-98. PMID: 1573291.

In 39 of 100 cancer patients admitted to the palliative care unit at Edmonton General Hospital, the presence of delirium during their last week of life required psychotropic drug treatment. In 10 of the 39 delirious patients, symptoms were only controllable by sedation; this was achieved in 9 patients by a continuous subcutaneous infusion of midazolam. Although haloperidol is considered to be the treatment of choice in agitated, delirious cancer patients, these data may suggest that palliative care treatment strategies for these patients may be different.