If the patient is not agitated, cyanosed nor imminently dying, a trial of methylphenidate (Ritalin®) 5–10mg or dextroamphetamine (Dexedrine®) 2.5–5.0mg once or twice daily in the morning may help. Tolerance develops to these drugs and may limit their role.

A newer CNS stimulant, modafinil (Alertec®) may be tried. Its mechanism of action is not entirely clear, but it has central 1-adrenergic receptor agonism. It also may have a different site of action in the hypothalamus rather than the cortex as in methylphenidate(5). As such, its adverse effect profile is also different and lower. Although officially approved only for use in narcolepsy, it has been found helpful in cancer-related fatigue, in Alzheimer's disease and as an adjuvant in depression(6). Dosage is 100–200mg morning or divided at morning and noon.

Confusion: Delirium and Dementia

Studies report that this symptom, which varies from mild to severe, occurs in 25–85% of patients with advanced cancer(7). Gagnon reported a prevalence of delirium in 52% of patients(8). On occasion, however, a few patients will remain coherent until within minutes or hours of death.

Lawlor et al(9) reported that, on admission to a palliative care unit, delirium was initially diagnosed in 42% of patients, and later developed in a further 45%, with 12% having no delirium at any point. Terminal delirium occurred in 88% of deaths.

Confusion about Confusion

In a Cochrane collaborative review, delirium is stated to be a common disorder that often complicates treatment in patients with life-limiting disease. Delirium is described using a variety of terms such as agitation, acute confusional state, encephalopathy, organic mental disorders and terminal restlessness(10).

Chang(11), in an editorial entitled *The Confusion About Confusion*, also notes various terms that are used but have different meanings, including confusion, altered mental state, cognitive impairment, acute brain syndrome, restlessness, dementia and delirium.

Even then, 'confusion' could represent delirium, pain, a psychiatric condition, dysphasia, dementia or disorientation(12). 'Altered mental status' could be agitation or anger, coma, seizures or delusions(13). 'Delirium' and 'dementia' are more closely defined using DSM-IV or ICD-10 coding. The criteria

for delirium by DSM-IV are listed in Chapter 17 Psychosocial Care, and by ICD-10 is shown in Table 14.1(14).

Acute brain syndrome(15) was often previously used but delirium has now replaced it(16).

Dementia will be briefly discussed later but, in comparison to delirium, has the following characteristics:

- Often irreversible
- Consciousness level usually not affected
- Hallucinations not common
- Usually deterioration of all cognitive and intellectual functions

Delirium in dementia appears to have similar diagnostic criteria(17).

N.B. For the purposes of this book, delirium will generally be used in place of confusion, and dementia used as it implies.

Etiology and Assessment of Delirium

Delirium is one of the most prevalent symptoms in palliative care and, since it may present in different shades of altered cognition, the routine use of screening instruments is recommended(18).

As with all symptoms, careful assessment is necessary in determining the etiology of confusion. Much can be gained by careful review of recent history, current medications and physical examination. Table 14.2 outlines the general causes of confusion in advanced disease.

Although the following data relates to a study (physicians, social workers)(11), Inouye et al report that hospice nurses have difficulty recognizing delirium, with a sensitivity of 18% (15–31%) but specificity of 95%(20). This means that they were accurate in knowing when delirium was not present, but significantly under-recognized it when

ICD-10 Diagnostic Guidelines for Delirium	
For a definite diagnosis, symptoms of mild or severe should be present in the following areas:	
• Impairment of consciousness and attention	• On a continuum from clouding to coma • Reduced ability to direct, focus, sustain and shift attention
• Global disturbance of cognition	• Perceptual distortions, illusions and hallucinations, most often visual • Impairment of abstract thinking and comprehension, with or without delusions, but typically with some degree of incoherence • Impairment of immediate recall and of recent memory but with relatively intact remote memory • Disorientation for time as well as, in more severe cases, for place and person
• Psychomotor disturbances	• Hypo- or hyperactivity and unpredictable shifts from one to the other • Increased reaction time • Increased or decreased flow of speech • Enhanced startle reaction
• Disturbance of sleep-wake cycle	• Insomnia or, in severe cases, total sleep loss or reversal of the sleep-wake cycle • Daytime drowsiness • Nocturnal worsening of symptoms • Disturbing dreams or nightmares, which may continue as hallucinations after wakening
• Emotional disturbances	• Examples - depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity
• The onset is usually rapid, the course diurnally fluctuating, and the total duration of the condition less than six months. • The above clinical picture is so characteristic that a fairly confident diagnosis of delirium can be made even if the underlying cause is not clearly established. • In addition to a history of an underlying physical or brain disease, evidence of cerebral dysfunction (e.g. EEG) may be required if the diagnosis is in doubt.	
Includes: • Acute brain syndrome • Acute confusional state • Acute infective psychosis • Acute organic reaction • Acute psycho-organic syndrome	

Table 14.1. ICD-10 Diagnostic Guidelines for Delirium. With permission WHO(14).

Causes of Delirium	
Physical Causes	• Tumor burden or location e.g. brain tumor • Infection, sepsis • Biochemical • Hypercalcemia • Uremia • Hepatic encephalopathy • Hypo- or hyperglycemia • Cardiorespiratory • Hypoxia • Hypercapnia • Cerebrovascular – e.g. stroke(19) • Trauma • Hemorrhage • Subdural hematoma • General discomfort
Drug Effects	• Idiosyncratic • Drug accumulation • Physical decline, decreased renal or hepatic clearance • Accidental or intentional overdose • Drug withdrawal • Opioid • Alcohol • Other medications e.g. steroid

Table 14.2. Causes of Delirium. M Downing

a patient was delirious. Four independent risk factors for under-recognition were identified: hypoactive delirium, age 80 years and older, vision impairment, and dementia. Under-recognition increased with the number of risk factors present from 2% (0 risk factors) – 6% (1 risk factor), 15% (2 risk factors), and 44% (3 or 4 risk factors). Patients with 3 or 4 risk factors had a 20-fold risk for under-recognition. Recognition of delirium can be enhanced with education in delirium features, cognitive assessment, and factors associated with poor recognition(20).

Any decision to carry out investigations must be weighed against the value which will be gained from the results and the expected improvement from treatment based on those tests, as well as the morbidity and 'usefulness' of pursuing investigations in a patient who may be deteriorating quickly and close to death.

Assessment Tools

There are many possible assessment tools used for assessing cognitive and affective aspects of delirium(21,22), although usual medical and nursing assessments may have similar outcomes(23). Of those, several are more often used in palliative care.

One of the most widely used tools for assessing cognition is the Folstein Mini Mental State Exam (MMSE)(24,25), but it is not specific for delirium. The Delirium Rating Scale (DRS)(26,27) has value in screening and monitoring the severity of delirium(21), as has the Memorial Delirium Assessment Scale (MDAS)(28,29).

Screening tools, i.e. not for full assessment, which could be used in various settings include Confusion Assessment Method (CAM)(8,30-34) and Bedside Confusion Scale (BCS)(35). Even then, use of these without some training reduces their sensitivity(36). CAM assesses 10 areas: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation and altered sleep-wake cycle. The CAM (short form) uses 4 factors: acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness.

Delirium Sub-types

Two types of delirium are of particular note as each is seen in end-of-life care(37). As the terms imply, hyperactive delirium involves an agitated, hyperalert stage, and hypoactive delirium involves being lethargic. Table 14.3 shows distinguishing characteristics.

Among older adults, especially those in long-term care situations, delirium may not appear to be very different from previous episodes observed when the resident experienced an infection, exacerbation of a chronic condition, anxiety, pain or adverse drug reactions. However, delirium at the end of life is usually multifactorial and exacerbated by the progressive multiple system failure.

Sandberg et al(38) reported that in the elderly, although episodes of delirium in general occur in the afternoon, evening or night, in fact 47% of the delirious patients in a residential facility had morning delirium. Further, nearly 26% were classified as having hypoactive, 30% as having hyperactive, and 42% as having mixed delirium(39).

Hypoactive delirium is often misdiagnosed in the elderly as depression or simply not recognized(40, 41).

The experience of delirium is highly distressful to most. In a recall study, Breitbart et al(42) found several important points:

- Patients who could recall delirium (about 53%) ranked their distress level at average 3.2 (scale 0–4) with delusions being the most distressful predictor
- Spouses/caregivers rated their distress at 3.75
- Nurses rated personal distress at 3.09 with symptom severity and perceptual disturbances as most distressful
- Patients with hypoactive delirium were just as distressed as those with hyperactive type
- They concluded stating the necessity for timely recognition and prompt treatment

Contrasting Features of Subtypes of Delirium		
Type	**Hyperactive Delirium**	**Hypoactive Delirium**
Symptoms	• Hallucinations • Delusions • Hyperarousal	• Sleepy • Withdrawn • Slowed
Examples	• Withdrawal syndromes (e.g. benzodiazepines, alcohol)	• Encephalopathies (hepatic, metabolic) • Benzodiazepine toxicity
Pathophysiology	• Elevated or normal cerebral metabolism • EEG – fast or normal • Reduced activity in GABA systems	• Decreased global cerebral metabolism • EEG – diffuse slowing • Overstimulation of GABA systems

Table 14.3. Contrasting Features of Subtypes of Delirium. From Handbook of Psychiatry in Palliative Medicine, edited by HM Chochinov, W Breibart. With permission of Oxford University Press, Inc(37).

Treatment

It is a major challenge to discern whether one should pursue investigations or not. If the cause could be identified easily, with minimal invasion and be readily treated with resulting improvement, then many would want this as this is a distressing symptom.

Physicians always face the dilemma of how aggressively to intervene in reversing delirium, and the following is a possible strategy(43):

- Identify the underlying cause (if possible) and assess its impact on the patient's quality of life
- Rank the distress of delirium in the context of the patient's overall symptom complex
- Assess the potential problems associated with correcting the underlying causes and consequent impact on quality of life (e.g. using IV line for antibiotics, and patient pulling out)
- Consider the advantages and disadvantages of intervention versus no intervention
- Discuss treatment options with the patient (if mild cognitive impairment) and the family to allow informed decision-making and ultimately the development of a consensus on the appropriate level of intervention

It is usually neither simple nor easy, and the causes are often multiple. When confronted with delirium in terminally ill or dying patients, health care professionals should always review a differential diagnosis and the likely factors involved. A firm diagnosis may only be attainable in less than half of cases(44). In the Lawlor study above(9) reversal of delirium was possible in 56% of first episodes, but only 26% if a subsequent delirium developed.

Factors associated with likely **reversible** delirium were:

- Opioid-induced neurotoxicity
- Psychoactive drugs
- Dehydration

Factors associated with **irreversibility**:

- Hypoxic encephalopathy
- Metabolic factors (e.g. hypercalcemia, hyponatremia, renal insufficiency)
- Non-respiratory infection

A valuable practical insight is that of a baseline vulnerability and superimposed precipitants. Age, mental status, multi-system impairment, decreased nutritional status and decreased functional status provide a precarious baseline. Any superimposed factor may then precipitate delirium, including medications, dehydration, infection, metabolic dysfunction or hypoxia.

The mortality rate in delirium varies of course by the etiology and patient condition, and varies from 10–65%(45).

Treatment Approaches

Taking the above facts into consideration, there are three approaches to consider in management as follows. Each of these have pros and cons, requiring team and family input as noted.

Additionally, similar to the relationship of pain and total pain, delirium has the underlying disease factors precipitating delirium, but there can be superimposed many other features, including unresolved fears, anxiety or spiritual journey. Cultural aspects may also be involved and respect for these are required as discussed in Chapters 17 Psychosocial Care and 18 Cultural and Spiritual Care.

The three possible treatment approaches include the intent to reverse delirium, the intent to relieve with sedation and the intent to observe for the time being.

1. Intent to Relieve by Reversal

In this approach, there is some likelihood of reversing delirium, particularly where the patient has a higher functional status.

Criteria for this include:

- Known patient wish for intervention where possible, even if chances are low
- If readily reversible
- If potentially reversible e.g. opioid neurotoxicity
- If not dying, i.e. earlier stages
- If dying, trial attempts – only if patient had wanted active treatments and reverse is likely; otherwise no. Treatment examples – hydration, O_2, opioid rotation

With this approach, some investigations and treatments will be carried out depending on the identified causes. Examples include antibiotics, hydration, bisphosphonates for hypercalcemia, oxygen, rotation of opioids, reduction or discontinuing of other offending drugs.

At the same time, low dose neuroleptics may be started. The aim is not to sedate, which may tip the situation to become irreversible, but rather to provide sufficient medication to reduce agitation. Therefore, one should use low-sedating neuroleptics and avoid anxiolytics as possible.

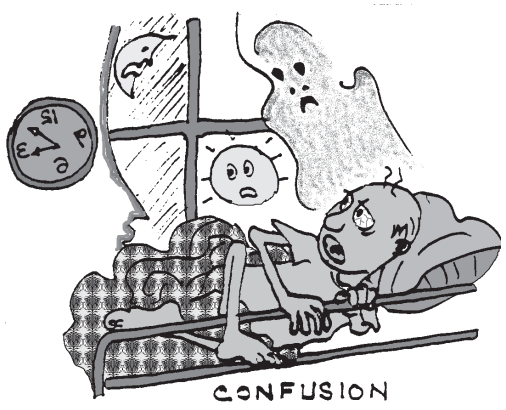
2. Intent to Relieve by Sedation

Reversal may be unrealistic or unwanted. Latimer(46) used the term 'sedation as therapy' in recognizing that the goal may be reduction of severity of delirium via use of sedative medication.

Criteria for this approach include:

- If delirium unpleasant and/or worsening
- If patient did not want active treatment
- If treatment is futile or unlikely to improve delirium
- If conditions are unsafe for patient, family or staff e.g. wild agitation, violence

In this approach, neuroleptics ± anxiolytics are titrated in the usual manner to provide acceptable control. Most patients will respond to this. This is not palliative sedation per se, as that is intended only in severe refractory symptoms. Palliative sedation as a topic is discussed in Chapter 19 Death and Dying with its own criteria.



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3. Intent to Observe Delirium

There are occasional times when, in known imminently dying patients, the patient develops hallucinations, visions or physical movements which appear comforting(37), or at least not disturbing, and possibly have interpretable meaning to family. This usually occurs in a hypoactive delirium, with its quietness. Some view this mild restlessness, visions and voices as a meaningful journey for the patient, with symbolism in the patient. Callanan's book *Final Gifts* discusses such types of experiences wherein some family find comfort(47).

In these cases, it may be prudent to observe the patient, provide support to family, but be prepared to initiate sedative therapy if circumstances change to agitation. As Breitbart and Cohen(37) note, "such a 'wait and see' approach must, however, be tempered by the knowledge that a lethargic or hypoactive delirium may very quickly and unexpectedly become an agitated delirium that can threaten the serenity and safety of the patient, family and staff."

At the same time, in the study discussed above(42), patients with hypoactive delirium who survived recalled that they were highly distressed during delirium. Guidance by the temporary substitute decision-maker and other family, along with the palliative care team, is needed to determine the most appropriate course of management.

Other Treatment Measures for Delirium

Provide Education and Support:

- Explanation (repeated) to patient, family and staff
- Stress that the patient is not going 'insane'
- There may be brief lucid periods for some meaningful interaction

Using More or Less Stimulation as Intervention:

Provide a safe and relaxing environment.
Patients with delirium need *LESS* stimulation:

- Quiet, well-lit room
- Minimal staff changes
- Repeated reassurance, explanation
- Calendars, clocks, observing sunshine, darkness, are helpful
- Contacts with fewer people
- Sedation as necessary

Patients with dementia need *MORE* stimulation, but **structured** so as not to further disorient:

- Constant reorientation to time, place
- Familiar and constant surroundings
- Sedation often worsens disorientation

Use of Relaxation Techniques

Some relaxation therapies may be helpful while others may worsen delirium. For example, massage, tub baths, gentle music, scripture, etc. may assist in calming the patient, while visualization or guided imagery can worsen hallucinations or deepen feelings of fear and dissociation from reality. Therefore, these need to be applied on an individual basis.

Drug Therapy in Delirium

Neuroleptics

Two classes of drugs can be used as indicated, neuroleptics and anxiolytics. Neuroleptic drugs are the standard and quite effective(48–50). There are the so-called 'conventional' and 'modern atypical' drugs with some being more sedating (e.g. chlorpromazine, methotrimeprazine, olanzapine) and others less so (e.g. haloperidol, quetiapine). Drugs in both categories are used for delirium management as discussed here, and also for intractable or refractory delirium as part of palliative sedation as discussed in Chapter 19 Death and Dying.

A Cochrane review(10) noted that evidence is scarce regarding this class of drugs in terminal care. Recognizing this limit, **haloperidol** is the most suitable drug therapy for the treatment of patients with delirium near the end of life. **Chlorpromazine** may be an acceptable alternative if a small risk of slight cognitive impairment is not a concern. This was based mainly on a study by Breitbart(51) but also with support from other case studies(52-56).

Haloperidol is generally considered the gold standard. It is a longer acting drug(48) which can be given PO, SC, IM or IV. In delirium, a suggested regimen is 0.5–1.5mg PO (mild), 1.5–5.0mg PO (severe) or 10mg SC or IV (very severe) [one report of up to 250mg/24hr(57)]. These doses may be repeated q30–60 minutes until alleviation (37,58). Once controlled, the maintenance dose suggested is 50% of amount to achieve control, usually between 1.5–20mg daily divided to 1–3 times daily. Typical doses in the first hour range from 0.5–20mg (45). Caution is needed in elderly patients who may need as little as 0.25–0.5mg q4h PRN(59), unless severe. **The parenteral dose should be 50% of the oral dose** (48). It does have a higher EPS profile and, if needed, benztropine is usually effective or lorazepam in selected cases where sedation is not an issue. Rare concerns are QT interval prolongation(59) or neuroleptic malignant syndrome(60).

Olanzapine is a newer atypical antipsychotic (61). It may be helpful where haloperidol is contraindicated(62). It has a low EPS profile but is more sedating. In one trial, 75% had complete response(63). Of those with poorer response, factors included age >70 years, history of dementia, central nervous system spread of cancer and hypoxia, 'hypoactive' delirium, and delirium of 'severe' intensity. Another reported value in the elderly who were non-responsive to other neuroleptics(64). There have been two case reports of opioid-induced delirium while on olanzapine, so its role in the multiple etiologies in palliative care remains unclear at present(65). Dosage is 2.5–10.0mg once to twice daily PO or by dissolvable wafer on the tongue(37) and also as injectable.

Methotrimeprazine is effective and used as an alternative to haloperidol(66,67). It is a higher sedation drug at doses of 15mg or above. It can be given PO, SC, IV as well as SL. Very low doses are used for nausea (0.5–2.5mg) but control of delirium usually requires 10–15mg for mild and up to 50mg for severe delirium. These may be given q4–8h initially, then less often once controlled(37).

Quetiapine may be an acceptable and safe alternative(68) but there is little evidence in the palliative field. Some have found it helpful at mean dosing of 93±23mg/day(69) or mean dosing of 44±30mg/day(70). Anecdotally, some have started at a low dose 6.25mg bid and increased as needed (71). For agitated dementia with delusions, an expert panel's first-line recommendation is an antipsychotic drug: risperidone (0.5–2.0 mg/day) was first line followed by quetiapine (50-150mg/day) and olanzapine (5.0–7.5mg/day) as high second-line options(72).

Other possible drugs are droperidol, risperidone, thioridazine or molindone.

In cases of *hypoactive delirium*, **methylphenidate** may be effective(73-75). Neuroleptics in low doses may also be effective alone(76) or in combination with methylphenidate in improving hypoactive delirium(77).

Anxiolytics

Benzodiazepine drugs do not clear the sensorium or improve cognition(45), and should not be used for delirium unless as an adjunct to primary therapy with haloperidol or anther neuroleptic(48). Lorazepam alone appears to be ineffective and is in fact associated with treatment-limiting adverse effects(78), but in combination may provide quicker and more effective control(78). Particular caution should be used in the elderly or those with hepatic failure.

The main role of this class is where haloperidol fails to control delirium, as in severe agitation or terminal restlessness. The goal in these cases is quiet

sedation only(38). In this situation, benzodiazepines give effective palliation of restlessness and, unlike haloperidol or other phenothiazines, do not exacerbate the existing tendency to myoclonus and convulsions(79).

Lorazepam is often used. It has an intermediate half-life, no active metabolites and several routes are available (SL, PO, SC, IV). Doses vary widely from 0.5mg to 5mg. In *mild* cases of delirium, it should be avoided as noted above or used on a PRN only basis for agitation until the neuroleptic provides overall control, especially if the goal is reversal of delirium.

In *severe* delirium with agitation and/or violent behavior, purposeful but hopefully temporary sedation is necessary, in which case both the neuroleptic and anxiolytic doses require escalation. Lorazepam may be 1–2–5mg SC q1h until control of agitation, then reduced as quickly as possible on a q4h basis.

Midazolam is also frequently used in delirium, but is more helpful for the restlessness aspect(79). In acute dosing, it is short-acting and rapidly effective. With longer-term infusion, the drug is widely redistributed and may result in prolonged effect(45). Initial dosing may be 5–10mg SC then 2–5mg SC PRN or by pump at 1–2–4mg/hr SC. Total daily doses have varied from 20–200mg/day(80,81).

In a review by Kehl(82), a number of studies demonstrated the effectiveness of other medications such as benzodiazepines (notably midazolam and lorazepam) or phenothiazines, either alone or in combinations. There is insufficient evidence to suggest that a single medication or class of medications is appropriate for terminal restlessness. There is a clear need for additional trials of neuroleptics, benzodiazepines, barbiturates and combination protocols to determine which protocols are the most effective and have the least side-effects(82).

Other Drugs

Propofol, a short-acting anesthetic, could also be used. Suggested starting doses are 10mg IV bolus, then 10mg/hr(83), or 20mg stat then 10–70mg/hr(84, 85).

Phenobarbital may be helpful(86,76) or in combination if midazolam fails to provide adequate sedation(67,88) in refractory cases.

Restlessness

Terminology and Etiology

This term is variously used in health care and thus, is often unclear. It may be defined as(89): 1) inability to rest or relax or be still, 2) the quality of being ceaselessly moving or active, or 3) a feeling of agitation expressed in motion.

In the broader context of palliative care, there are several categories in which restlessness may be evident:

- **Physical** – pain, constipation, bladder retention, hypoxia, metabolic, organ failure, fever, etc.
- **Drug** effect – EPS akathisia, opioid-induced neurotoxicity, etc.
- **Psychosocial** – personal suffering, existential anguish, interpersonal conflict, spiritual journey, worry, grief, etc.
- **Psychiatric** – delirium of any cause, dementia, anxiety disorder, psychosis, etc.
- Imminently **dying** – any combination of above with altered, fluctuating and declining state of consciousness

Kehl(82) lists several terms used in the literature to describe the latter in dying patients, including terminal delirium, terminal restlessness, terminal agitation, terminal anguish and confusion at end-of-life.

As readily appreciated, each of these categories and sub-issues require assessment and, generally speaking, separate strategies for relief. Sometimes, however, the strategy is even 'not to relieve' per se, as this may reflect an important emotional process for the patient.

References

1. Ingham JM, Layman-Goldstein M, Derby S, et al. The characteristics of the dying process in cancer patients in a hospice center. Proceedings of Annual Meeting, American Society of Clinical Oncology 1994;13:172.
2. Twycross R, Lack S. Persistent Excessive Drowsiness: Table 9.5. In: Symptom Control in Far Advanced Cancer: Pain Relief. London: Pitman Publishing Limited; 1983.
3. Latimer E. Ethical care at the end of life. Canadian Medical Association Journal 1998;158(13):1741-1747.
4. Kuhl DK, Wilensky P. Decision making at end of life: a model using an ethical grid and principles of group process. Journal of Palliative Medicine 1999;2(1):75-86.
5. Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. Proceedings of the National Academy of Sciences of the United States of America 1996;93(24):14128-33.
6. Cox JM, Pappagallo M. Modafinil: a gift to portmanteau. American Journal of Hospice & Palliative Care 2001;18(6):408-10.
7. Breitbart W, Bruera E, Chochinov H, Lynch M. Neuropsychiatric syndromes and psychological symptoms in patients with advanced cancer. Journal of Pain & Symptom Management 1995;10(2):131-150.
8. Gagnon P, Allard P, Masse B, DeSerres M. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis, and continuous monitoring. Journal of Pain & Symptom Management 2000;19(6):412-26.
9. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. [see comment]. Archives of Internal Medicine 2000;160(6):786-94.
10. Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. Cochrane Database of Systematic Reviews 2004(2):CD004770.
11. Chang VT. The confusion about confusion. [see comment]. Journal of Palliative Medicine 2002;5(5):659-660.
12. Johnson MH. Assessing confused patients. Journal of Neurology, Neurosurgery & Psychiatry 2001;71 Suppl 1:i7-12.
13. Tuma R, DeAngelis LM. Altered mental status in patients with cancer. [see comment]. Archives of Neurology 2000;57(12):1727-1731.
14. WHO. ICD-10 Diagnostic Guidelines. from Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: WHO Publications; 1992.
15. Stedeford A. Confusional states, a paper. Oxford: Sir Michael Sobell House.
16. Roche V. Southwestern Internal Medicine Conference. Etiology and management of delirium. American Journal of the Medical Sciences 2003;325(1):20-30.
17. Trzepacz PT, Mulsant BH, Amanda Dew M, Pasternak R, Sweet RA, Zubenko GS. Is delirium different when it occurs in dementia? A study using the delirium rating scale. Journal of Neuropsychiatry & Clinical Neurosciences 1998;10(2):199-204.
18. Carceni A, Bosisio M. Acute confusional states. In: Voltz R, Bernat JL, Borasio GD, Maddocks I, Oliver D, Portenoy R, editors. Palliative Care in Neurology. New York: Oxford University Press; 2004. p. 228-240.
19. Caeiro L, Ferro JM, Claro MI, Coelho J, Albuquerque R, Figueira ML. Delirium in acute stroke: a preliminary study of the role of anticholinergic medications. European Journal of Neurology 2004;11(10):699-704.
20. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM, Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Archives of Internal Medicine 2001;161(20):2467-73.
21. Schuurmans MJ, Deschamps PI, Markham SW, Shortridge-Baggett LM, Duursma SA. The measurement of delirium: review of scales. Research & Theory for Nursing Practice 2003;17(3):207-24.
22. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. Journal of Pain & Symptom Management 1995;10(1):35-77.
23. Cole MG, McCusker J, Bellavance F, Primeau FJ, Bailey RF, Bonnycastle MJ, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial.[see comment]. Canadian Medical Association Journal 2002;167(7):753-9.
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12(3):189-98.
25. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 1997;79(4):835-42.
26. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Research 1988;23:89-97.
27. Trzepacz PT. The Delirium Rating Scale. Its use in consultation-liaison research. Psychosomatics 1999;40(3):193-204.
28. Lawlor PG, Nekolaichuk C, Gagnon B, Mancini IL, Pereira JL, Bruera ED. Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: Assessing delirium in advanced cancer. Cancer 2000;88(12):2859-67.
29. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale.[see comment]. Journal of Pain & Symptom Management 1997;13(3):128-37.
30. 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.[see comment]. Annals of Internal Medicine 1990;113(12):941-8.
31. Monette J, Galbaud du Fort G, Fung SH, Massoud F, Moride Y, Arsenault L, et al. Evaluation of the Confusion Assessment Method (CAM) as a screening tool for delirium in the emergency room. General Hospital Psychiatry 2001;23(1):20-5.
32. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[see comment]. Critical Care Medicine 2001;29(7):1370-9.
33. Laplante J, Cole MG. Detection of delirium using the confusion assessment method. Journal of Gerontological Nursing 2001;27(9):16-23.
34. Gonzalez M, de Pablo J, Fuente E, Valdes M, Peri JM, Nomdedeu M, et al. Instrument for detection of delirium in general hospitals: adaptation of the confusion assessment method. Psychosomatics 2004;45(5):426-31.
35. Sarhill N, Walsh D, Nelson KA, LeGrand S, Davis MP. Assessment of delirium in advanced cancer: the use of the bedside confusion scale. American Journal of Hospice & Palliative Care 2001;18(5):335-41.
36. Rolfson DB, McElhaney JE, Jhangri GS, Rockwood K. Validity of the confusion assessment method in detecting postoperative delirium in the elderly. International Psychogeriatrics 1999;11(4):431-8.
37. Breitbart W, Cohen K. Delirium in the terminally ill. In: Chochinov H, Breitbart W, editors. Handbook of Psychiatry in Palliative Medicine. New York: Oxford University Press; 2000. p. 75-90.
38. Sandberg O, Gustafson Y, Brannstrom B, Bucht G. Clinical profile of delirium in older patients. [see comment]. Journal of the American Geriatrics Society 1999;47(11):1300-6.

39. Meagher DJ, O'Hanlon D, O'Mahony E, Casey PR, Trzepacz PT. Relationship between symptoms and motoric subtype of delirium. Journal of Neuropsychiatry & Clinical Neurosciences 2000;12(1):51-6.
40. Farrell KR, Ganzini L. Misdiagnosing delirium as depression in medically ill elderly patients. Archives of Internal Medicine 1995;155(22):2459-64.
41. Goy E, Ganzini L. Delirium, anxiety and depression. In: Morrison RS, Meier DE, Capello C, editors. Geriatric Palliative Care. New York: Oxford University Press; 2003. p. 286-303.
42. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers and their nurses. Psychosomatics 2002;13(3):183-194.
43. Yennurajalingam S, Braitech F, Bruera E. Pain and delirium research in the elderly. Clinics in Geriatric Medicine 2005;21:93-119.
44. Bruera E, Miller L, McCallion J, Macmillan K, Krefting L, Hanson J. Cognitive failure in patients with terminal cancer: a prospective study. Journal of Pain & Symptom Management 1992;7(4):192-5.
45. Ingham JM, Carceni A. Delirium. In: Berger AM, Portenoy R, Weisman H, editors. Principles and Practice of Palliative Care and Supportive Oncology. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 555-576.
46. Latimer E. Managing delirium in seriously ill and dying patients. Canadian Journal of CME 1999 September.
47. Callanan M, Kelley P. Final Gifts. New York: Poseidon Press; 1992.
48. Vella-Brincat J, Macleod AD. Haloperidol in palliative care. Palliative Medicine 2004;18(3):195-201.
49. Bruera E, Franco JJ, Maltoni M, Watanabe S, Suarez-Almazor M. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. Journal of Pain & Symptom Management 1995;10(4):287-91.
50. Adams F. Emergency intravenous sedation of the delirious, medically ill patient. Journal of Clinical Psychiatry 1988;49 Suppl:22-7.
51. Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. American Journal of Psychiatry 1996;153(2):231-7.
52. Bluestine S, Lesko L. Psychotropic medications in oncology and in AIDS patients. Advances in Psychosomatic Medicine 1994;21:107-37.
53. Carceni A. Delirium in palliative care. European Journal of Palliative Care 1995;2:62-67.
54. Fainsinger R, Bruera E. Treatment of delirium in a terminally ill patient. Journal of Pain & Symptom Management 1992;7(1):54-6.
55. Fainsinger RL, Tapper M, Bruera E. A perspective on the management of delirium in terminally ill patients on a palliative care unit. Journal of Palliative Care 1993;9(3):4-8.
56. Roth AJ, Breitbart W. Psychiatric emergencies in terminally ill cancer patients. Hematology - Oncology Clinics of North America 1996;10(1):235-59.
57. Adams F. Emergency intravenous sedation of the delirious, medically ill patient. Journal of Clinical Psychiatry 1988 49 Suppl:22-27.
58. Adams F, Fernandez F, Andersson BS. Emergency pharmacotherapy of delirium in the critically ill cancer patient. Psychosomatics 1986;27(1 Suppl):33-8.
59. Practice guideline for the treatment of patients with delirium. American Psychiatric Association. www.psych.org. American Journal of Psychiatry 1999;156(5 Suppl):1-20.
60. Chandran GJ, Mikler JR, Keegan DL. Neuroleptic malignant syndrome: case report and discussion.[see comment]. Canadian Medical Association Journal 2003;169(5):439-42.
61. Khojainova N, Santiago-Palma J, Kornick C, Breitbart W, Gonzales GR. Olanzapine in the management of cancer pain. Journal of Pain & Symptom Management 2002;23(4):346-50.
62. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting.[see comment]. Intensive Care Medicine 2004;30(3):444-9.
63. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002;43(3):175-82.
64. Solomons K, Geiger O. Olanzapine use in the elderly: a retrospective analysis. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 2000;45(2):151-5.
65. Estfan B, Yavuzsen T, Davis M. Development of opioid-induced delirium while on olanzapine: a two-case report. Journal of Pain & Symptom Management 2005;29(4):330-2.
66. Patt RB, Proper G, Reddy S. The neuroleptics as adjuvant analgesics. Journal of Pain & Symptom Management 1994;9(7):446-53.
67. Sykes N, Thorns A. Sedative use in the last week of life and the implications for end-of-life decision making. Archives of Internal Medicine 2003;163(3):341-4.
68. Pae CU, Lee SJ, Lee CU, Lee C, Paik IH. A pilot trial of quetiapine for the treatment of patients with delirium. Human Psychopharmacology 2004;19(2):125-7.
69. Kim KY, Bader GM, Kotlyar V, Gropper D. Treatment of delirium in older adults with quetiapine. Journal of Geriatric Psychiatry & Neurology 2003;16(1):29-31.
70. Sasaki Y, Matsuyama T, Inoue S, Sunami T, Inoue T, Denda K, et al. A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium. Journal of Clinical Psychiatry 2003;64(11):1316-21.
71. Black F. Quetiapine dosage in delirium. In. Victoria; 2005.
72. Alexopoulos GS, Streim J, Carpenter D, Docherty JP, Expert Consensus Panel for Using Antipsychotic Drugs in Older P. Using antipsychotic agents in older patients. Journal of Clinical Psychiatry 2004;65 Suppl 2:5-99; discussion 100-102; quiz 103-4.
73. Morita T, Otani H, Tsunoda J, Inoue S, Chihara S. Successful palliation of hypoactive delirium due to multi-organ failure by oral methylphenidate. Supportive Care in Cancer 2000;8(2):134-7.
74. Gagnon B, Low G, Schreier G. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. Journal of Psychiatry & Neuroscience 2005;30(2):100-7.
75. Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliative Medicine 2004;18(3):184-94.
76. Platt MM, Breitbart W, Smith M, Marotta R, Weisman H, Jacobsen PB. Efficacy of neuroleptics for hypoactive delirium. Journal of Neuropsychiatry & Clinical Neurosciences 1994;6(1):66-7.
77. Stiefel F, Bruera E. Psychostimulants for hypoactive-hypoalert delirium? Journal of Palliative Care 1991;7(3):25-6.
78. Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. American Journal of Psychiatry 1996;153(2):231-7.
79. Burke AL. Palliative care: an update on "terminal restlessness". Medical Journal of Australia 1997;166(1):39-42.
80. Bottomley DM, Hanks GW. Subcutaneous midazolam infusion in palliative care. Journal of Pain & Symptom Management 1990;5(4):259-61.
81. Burke AL, Diamond PL, Hulbert J, Yeatman J, Farr EA. Terminal restlessness--its management and the role of midazolam.[see comment]. Medical Journal of Australia 1991;155(7):485-7.
82. Kehl KA. Treatment of terminal restlessness: a review of the evidence. Journal of Pain & Palliative Care Pharmacotherapy 2004;18(1):5-30.
83. Casarett DJ, Inouye SK, American College of Physicians-American Society of Internal Medicine End-of-Life Care Consensus P. Diagnosis and management of delirium near the end of life.[see comment]. Annals of Internal Medicine 2001;135(1):32-40.

84. Moyle J. The use of propofol in palliative medicine. Journal of Pain & Symptom Management 1995;10(8):643-6.
85. Mercadante S, De Conno F, Ripamonti C. Propofol in terminal care. Journal of Pain & Symptom Management 1995;10(8):639-42.
86. Twaddle ML. The process of dying and managing the death event. Primary Care: Clinics in Office Practice 2001;28(2):329-338.
87. Stirling LC, Kurowska A, Tookman A. The use of phenobarbitone in the management of agitation and seizures at the end of life.[see comment]. Journal of Pain & Symptom Management 1999;17(5):363-8.
88. Cheng C, Roemer-Becuwe C, Pereira J. When midazolam fails. Journal of Pain & Symptom Management 2002;23(3):256-65.
89. Definition of 'restlessness'. In: www.wordreference.com/definition/restlessness. Princeton University; 2003.
90. Brajtman S. The impact on the family of terminal restlessness and its management. Palliative Medicine 2003;17(5):454-60
91. Brajtman S. Terminal restlessness: perspectives of an interdisciplinary palliative care team. International Journal of Palliative Nursing 2005;11(4):170 .
92. Cherny N, Portenoy R. Sedation in the management of refractory symptoms; guidelines for evaluation and treatment. Journal of Palliative Care 1994;10(2):31-38.
93. Wanzer S, Federman D, Adlelstein S, et al. The physician's responsibility toward hopelessly ill patients - a second look. New England Journal of Medicine 1989;120:844-849.
94. Smith R. Ethical issues in cancer pain. In: Chapman C, Foley K, editors. Current and Emergency Issues in Cancer Pain: Research and Practice. New York: Raven Press; 1993. p. 385-392.
95. Lloyd Williams M, Payne S. A qualitative study of clinical nurse specialists' views on depression in palliative care patients. Palliative Medicine 2003;17(4):334-8.
96. Wilson KG, Chochinov HM, de Faye BJ, Breitbart W. Diagnosis and management of depression in palliative care. In: Chochinov HM, Breitbart W, editors. Handbook of Psychiatry in Palliative Medicine. Toronto: Oxford University Press; 2000. p. 25-49.
97. Hotopf M, Chidgey J, Addington-Hall J, Ly KL. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. Palliative Medicine 2002;16(2):81-97.
98. Beck A, Beck R. Screening depressed patients in family practice: a rapid technique. Postgraduate Medicine 1972;52:81-85.
99. Passik SD, Lundberg JC, Rosenfeld B, Kirsh KL, Donaghy K, Theobald D, et al. Factor analysis of the Zung Self-Rating Depression Scale in a large ambulatory oncology sample. Psychosomatics 2000;41(2):121-7.
100. Lloyd Williams M. Screening for depression in palliative care patients. In: Lloyd Williams M, editor. Psychosocial Issues in Palliative Care. Oxford: Oxford University Press; 2003. p. 105-118.
101. Chochinov HM, Wilson KG, Enns M, Lander S. "Are you depressed?" Screening for depression in the terminally ill.[see comment]. American Journal of Psychiatry 1997;154(5):674-6.
102. Lloyd-Williams M, Spiller J, Ward J. Which depression screening tools should be used in palliative care? Palliative Medicine 2003;17(1):40-3.
103. Mahoney J, Drinka TJ, Abler R, Gunter-Hunt G, Matthews C, Gravenstein S, et al. Screening for depression: single question versus GDS.[see comment]. Journal of the American Geriatrics Society 1994;42(9):1006-8.
104. Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression. Two questions are as good as many.[see comment]. Journal of General Internal Medicine 1997;12(7):439-45.
105. Brody DS, Hahn SR, Spitzer RL, Kroenke K, Linzer M, deGruy FV, 3rd, et al. Identifying patients with depression in the primary care setting: a more efficient method. Archives of Internal Medicine 1998;158(22):2469-75.
106. Robinson JA, Crawford GB. Identifying palliative care patients with symptoms of depression: an algorithm. Palliative Medicine 2005;19(4):278-87.
107. Maguire P, Hopwood P, Tarrier N, Howell T. Treatment of depression in cancer patients. Acta Psychiatrica Scandinavica, Supplementum 1985;320:81-4.
108. Pessin H, Potash M, Breitbart W. Diagnosis, assessment and treatment of depression in palliative care. In: Lloyd Williams M, editor. Psychosocial Issues in Palliative Care. Oxford: Oxford University Press; 2003. p. 81-103.
109. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. Journal of Clinical Psychiatry 1989;50(7):241-9.
110. Homsi J, Nelson KA, Sarhill N, Rybicki L, LeGrand SB, Davis MP, et al. A phase II study of methylphenidate for depression in advanced cancer. American Journal of Hospice & Palliative Care 2001;18(6):403-7.
111. Burns MM, Eisendrath SJ. Dextroamphetamine treatment for depression in terminally ill patients. Psychosomatics 1994;35(1):80-3.
112. Breitbart W, Mermelstein H. Pemoline. An alternative psychostimulant for the management of depressive disorders in cancer patients. Psychosomatics 1992;33(3):352-6.
113. Caraceni A, Simonetti F. Psychostimulants: new concepts for palliative care from the modafinil experience? Journal of Pain & Symptom Management 2004;28(2):97-9.
114. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. Journal of Clinical Psychiatry 2000;61(5):378-81.
115. BCCA. Prevalence of cancer by type. http://www.bccancer.bc.ca/HPI/CancerStatistics. In: British Columbia Cancer Agency; 2004.
116. Ziai WC, Hagen N. Headache and other neurologic complications. In: Berger AM, Portenoy RK, Weissman DE, editors. Principles and Practice of Palliative Care and Supportive Oncology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 515-531.
117. O'Neill BP, Buckner JC, Coffey RJ, Dinapoli RP, Shaw EG. Brain metastatic lesions. Mayo Clinic Proceedings 1994;69(11):1062-8.
118. Metastatic tumors to the brain and spine. http://neurosurgery.mgh.harvard.edu/abta/mets.htm. In: American Brain Tumor Association; 1993.
119. Peterson K. Neoplasms. In: Voltz R, Bernat JL, Borasio GD, Maddocks I, Oliver D, Portenoy R, editors. Palliative Care in Neurology. New York: Oxford University Press; 2004. p. 37-47.
120. Das A, Hochberg FH. Clinical presentation of intracranial metastases. Neurosurgery Clinics of North America 1996;7(3):377-91.
121. http://oncologychannel.com/braincancer/. In: monitored by Healthcommunities.com; 2005.
122. Larsson S. Palliative radiation. In: Palliative Care Medical Intensive Course, editor. Victoria Hospice Society 2004.
123. Weil S, Noachtar S. Epileptic seizures and myoclonus. In: Voltz R, Bernat JL, Borasio GD, Maddocks I, Oliver D, Portenoy R, editors. Palliative Care in Neurology. New York: Oxford University Press; 2004. p. 178-186.
124. Byrne T. Spinal cord compression from epidural metastases. New England Journal of Medicine 1992;327(9):614-619.
125. Benjamin R. Neurologic complications of prostate cancer. American Family Physician 2002;65(9):1834-40.
126. Joseph M, Tayar R. Spinal cord compression requires early detection. European Journal of Palliative Care 2005;12(4):141-143.
127. Hill ME, Richards MA, Gregory WM, Smith P, Rubens RD. Spinal cord compression in breast cancer: a review of 70 cases. British Journal of Cancer 1993;68(5):969-73.
128. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Journal of Clinical Oncology 2005;23(9):2028-37.