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

<table>
<thead>
<tr>
<th>For a definite diagnosis, symptoms of mild or severe should be present in the following areas:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Impairment of consciousness and attention</td>
</tr>
<tr>
<td>• On a continuum from clouding to coma</td>
</tr>
<tr>
<td>• Reduced ability to direct, focus, sustain and shift attention</td>
</tr>
<tr>
<td>• Global disturbance of cognition</td>
</tr>
<tr>
<td>• Perceptual distortions, illusions and hallucinations, most often visual</td>
</tr>
<tr>
<td>• Impairment of abstract thinking and comprehension, with or without delusions, but typically with some degree of incoherence</td>
</tr>
<tr>
<td>• Impairment of immediate recall and of recent memory but with relatively intact remote memory</td>
</tr>
<tr>
<td>• Disorientation for time as well as, in more severe cases, for place and person</td>
</tr>
<tr>
<td>• Psychomotor disturbances</td>
</tr>
<tr>
<td>• Hypo- or hyperactivity and unpredictable shifts from one to the other</td>
</tr>
<tr>
<td>• Increased reaction time</td>
</tr>
<tr>
<td>• Increased or decreased flow of speech</td>
</tr>
<tr>
<td>• Enhanced startle reaction</td>
</tr>
<tr>
<td>• Disturbance of sleep-wake cycle</td>
</tr>
<tr>
<td>• Insomnia or, in severe cases, total sleep loss or reversal of the sleep-wake cycle</td>
</tr>
<tr>
<td>• Daytime drowsiness</td>
</tr>
<tr>
<td>• Nocturnal worsening of symptoms</td>
</tr>
<tr>
<td>• Disturbing dreams or nightmares, which may continue as hallucinations after wakening</td>
</tr>
<tr>
<td>• Emotional disturbances</td>
</tr>
<tr>
<td>• Examples - depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity</td>
</tr>
<tr>
<td>• The onset is usually rapid, the course diurnally fluctuating, and the total duration of the condition less than six months.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
</tbody>
</table>

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).
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, 50% 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

### 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

---

### Table 14.3. Contrasting Features of Subtypes of Delirium

<table>
<thead>
<tr>
<th>Type</th>
<th>Hyperactive Delirium</th>
<th>Hypoactive Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>• Hallucinations</td>
<td>• Sleepy</td>
</tr>
<tr>
<td></td>
<td>• Delusions</td>
<td>• Withdrawn</td>
</tr>
<tr>
<td></td>
<td>• Hyperarousal</td>
<td>• Slowed</td>
</tr>
<tr>
<td>Examples</td>
<td>• Withdrawal syndromes (e.g. benzodiazepines, alcohol)</td>
<td>• Encephalopathies (hepatic, metabolic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Benzodiazepine toxicity</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>• Elevated or normal cerebral metabolism</td>
<td>• Decreased global cerebral metabolism</td>
</tr>
<tr>
<td></td>
<td>• EEG – fast or normal</td>
<td>• EEG – diffuse slowing</td>
</tr>
<tr>
<td></td>
<td>• Reduced activity in GABA systems</td>
<td>• Overstimulation of GABA systems</td>
</tr>
</tbody>
</table>

From Handbook of Psychiatry in Palliative Medicine, edited by HM Chochinov, W Breibart. With permission of Oxford University Press, Inc(37).
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, 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.
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, benzotripine 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 another 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.

---

**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


86. Twaddle ML. The process of dying and managing the death event. Primary Care: Clinics in Office Practice 2001;28(2):329-338.