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KEYWORDS

- Delirium • Encephalopathy • Acute mental status change • Confusion • Elderly

KEY POINTS

- Delirium is a geriatric syndrome characterized by acute confusion and inattention that may persist in a subacute form lasting for weeks or even months.
- Delirium is a manifestation of an underlying condition and is often considered multifactorial. Common causes in elderly patients include infections, urinary retention, pain, and medication side effects. Finding and treating the underlying causes are key to resolving delirium.
- Delirium has significant morbidity and mortality. It not only increases risk of falls and prolonged hospitalization, it may result in irreversible cognitive decline and even death.
- Because of its association with dementia and poor outcomes, delirium is an important geriatric syndrome for primary care providers to know as they care for an increasing geriatric population.

INTRODUCTION

Delirium is a common neurocognitive disorder characterized by an acute change in cognition, attention, and consciousness that results in what experts describe as brain failure. Delirium has traditionally been discussed in the acute-care setting, where it occurs in up to 80% of patients.¹ Despite much lower incidence of delirium in outpatient care areas, population aging makes it more likely that primary care providers will encounter patients with delirium. These trends, combined with delirium's high morbidity and mortality, make delirium an important topic that primary providers should not ignore.

Delirium is known by a variety of different terms, including altered mental status, acute mental status change, encephalopathy, agitation, altered level of consciousness,

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brain failure, and even psychosis. Although these terms are descriptive of symptoms, the ongoing use of so many different terms can be confusing to trainees, providers, and families. In addition, the lack of a clear pathologic process and the slowness of many practitioners to adopt validated diagnostic methods has resulted in continued underdiagnosis.²

Delirium has been vaguely described for more than 2 centuries, but it has only been formally defined since the mid-1990s by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Earlier editions described organic psychosis symptoms, whereas later editions (DSM-IV and DSM-V) describe it more specifically as an acute change in mental status with a fluctuating course, inattention, disturbance of consciousness, and disorganized thinking.³ The DSM has become the gold standard from which various screens and assessment criteria have been formulated in an effort to make bedside diagnosis easier and more efficient.

Delirium is not only common but also has a significant health care burden. Although 30% to 40% is preventable,^{4–6} once it occurs, delirium results in increased debility and loss of function as well as increased morbidity and mortality and health care costs,^{7–12} making it a significant public health burden costing more than \$164 billion annually in the United States alone.¹²

EPIDEMIOLOGY

The overall prevalence of delirium varies widely, between 9% and 80% by setting, with lower levels among outpatient and residential care homes.^{1,10–13} The lowest incidence occurs in the outpatient office setting, at only 2%,^{10,13} but this is expected to increase with population aging and age-associated increases in multimorbidity and dementia.^{14,15} In addition, patients presenting with delirium almost always require emergency medical care or hospital admission. Among elderly patients presenting to emergency departments (EDs), up to 17% of all community-dwelling seniors and 40% of nursing home residents present with this diagnosis.¹⁶

Patients requiring hospital admission, between 18% and 35% of patients had a diagnosis of delirium on admission.^{1,16} Once hospitalized, elderly patients have a high risk of developing delirium, especially if they have an underlying dementia disorder. Those in postoperative wards, intensive care units (ICUs), geriatric wards, and hospice wards had the highest prevalence of delirium 50% to 80%.^{10,11,13,16,17} Delirium is also prevalent in the skilled nursing facilities and postacute care (PAC) settings after discharge from acute hospitalization, with more than 9% of patients having documented evidence of delirium on admission to PAC facilities.¹⁸ This situation leads to an overall delirium rate of 29% to 64% for older adult patients.¹

Patients who develop delirium are at increased risk for a variety of poor outcomes, including falls, catheter-associated infections, and debility, as well as prolonged hospital stay, and increased likelihood of physical restraints and antipsychotic medication administration. Patients who develop delirium in the ICU are at 2 to 4 times increased risk for death both during and after hospitalization^{13,19,20}; those on general medicine or surgical wards have a 1.5-fold increased risk of death in the year after hospitalization.^{21–23} Patients visiting the ED who are diagnosed with delirium have up to 70% increased risk of death in the first 6 months after their visit.²⁴

Aging

Although cognitive loss is not a normal aging phenomenon, the development of cognitive loss such as dementia occurs more commonly with aging. Autopsy

studies indicate that as many as half of all older adults (>80 years old) have changes consistent with Alzheimer disease at death.^{25,26} As previously mentioned, with the aging population and increasing rates of multimorbidity, more patients will be living longer with precursor risks for dementia and therefore delirium.^{14,15} Primary care providers will be expected to care for more older patients with dementia and therefore delirium.

It is common for patients with undiagnosed dementia to be diagnosed with delirium while hospitalized or acutely ill. Delirium in patients without a previous diagnosis of dementia may be a red flag to suggest underlying cognitive loss.^{27,28} In addition, patients with dementia have more significant decline when they develop delirium compared with patients with no underlying cognitive deficits.^{29–32} Preexisting cognitive disorders lower the threshold for delirium. This is why patients with dementia are more prone to develop delirium from what would otherwise be an uncomplicated urinary tract infection. Unfortunately, delirium can result in cognitive impairment like dementia in patients without prior cognitive deficits.³³

ASSESSMENT

Delirium is diagnosed clinically as there are currently no laboratory or radiological studies available to confirm its presence. Most physicians find the DSM cumbersome and time consuming as they are not trained in its use and have increasingly limited time with patients. To combat this problem, several diagnostic tools have been developed to allow clinicians to diagnose delirium more efficiently and effectively.³⁴

Similarly educating nurses to identify delirium has been shown to be effective as nurses in acute and post-acute care settings have more contact with the patients on a daily basis than physicians.³⁵ Screening tests such as the Nursing Delirium Screening scale (Nu-DESC), Delirium Observational Screening scale (DOS), and NEECHAM have been used to evaluate delirium risk, but are not diagnostic.^{36–38} They are mostly used by nursing staff to predict individual patients' risks for developing delirium in the acute-care setting. However, tools such as the confusion assessment method (CAM)³⁹ and the 4-AT⁴⁰ useful in diagnosing delirium. The CAM is the most commonly used tool, especially in its short form, which simplifies its use at the bedside.⁴¹ The 4-AT in the U.S., a newer tool, is also gaining acceptance especially in the U.K. where it was developed. **Fig. 1** shows the flow used

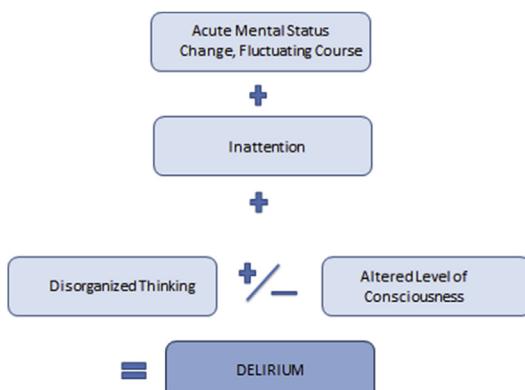


Fig. 1. CAM criteria for delirium diagnosis. (Data from Inouye SK. Short CAM: Training manual and Coding Guide. 2014; Boston: Hospital Elder Life Program.)

by the CAM short form. The CAM can be accessed at www.hospitalelderlifeprogram.org and the 4-AT at www.scottishdeliriumassociation.com. The 4-AT can also be viewed in [Appendix 1](#).

In addition to the original and short versions of the CAM, an ICU version^{42,43} has been validated specifically for use in critical care wards and EDs. The use of a tool is very important in diagnosing delirium regardless of which one is used. Research has shown that providers lack knowledge of delirium and underdiagnose when tools are not used.⁴⁴⁻⁴⁶

Identification of an organic underlying cause is also important in diagnosing and treating delirium.⁴⁷ Identifying an underlying organic cause helps differentiate delirium from psychosis, a non-organic, psychiatric disorder. This distinction also helps distinguish the behavioral disturbances often associated with dementia from delirium. Pearls for evaluation are listed in [Fig. 2](#).

Careful review of the diagnostic criteria of delirium aids in making this distinction. Although patients with dementia may be confused, their confusion should not occur



Fig. 2. General evaluation of delirium. Note that several emergent or more urgent tests, such as electrocardiogram, arterial blood draws, and chest computed tomography (CT), have been omitted because they should be performed in an ED after appropriate triage. CBC, complete blood count; CMP, complete metabolic profile; CXR, chest radiograph; EEG, electroencephalogram; pt, patient; TSH, thyroid-stimulating hormone; UA, urinalysis; XR, radiograph.

acutely nor should it have a fluctuating course. The exception to this is Lewy body dementia, which can have fluctuations in course as well as inattention.⁴⁸ However, patients with dementia can hold attention and organize their thoughts, compared with delirious patients who cannot. Care should be taken in making this distinction in the outpatient office. Delirium should be considered an urgent, if not emergent, situation requiring appropriate triage and referral.

PATOPHYSIOLOGY

The pathophysiology of delirium is extremely complex and still not well understood. Each individual patient with delirium has a unique set of underlying causes contributing to their symptoms.^{49–51} The interplay between a patient's existing pathophysiology and the changes occurring with an acute illness result in an imbalance of brain chemistry. Although the individual predisposing factors, acute illness, pathways, and chemicals involved may vary, the result is the same, acute brain failure. Factors involved in delirium pathophysiology can be separated into preexisting risk factors and predisposing actors which are listed in **Table 1**.

Older patients, especially those over 80 years old, are at increased risk, as are patients with genetic predispositions. Although the genetic predispositions are not well known, age seems to predispose to delirium development in its association with an increased incidence of dementia.^{32,33} As a cohort, older patients also have more comorbidities as a cohort compared with younger patients and therefore take more medications. The increased burden of adverse side effects and the number of medications taken has also been shown to contribute to delirium occurrence.^{51–55}

Metabolic derangements are common causes of delirium.^{49,56} Alterations in electrolytes such as sodium and potassium, as well as glucose imbalances, are commonly seen in this role. Dehydration, uremia, and hepatic dysfunction also contribute to delirium, as does hypoxia and hypercapnia.^{49,56,57} Some of these factors, like glucose, directly affect the brain's ability to function, whereas others, like dehydration and inflammatory cascades, work more indirectly.^{58–60} Inflammation works this way by causing cytokine activation, which in turn leads to impaired blood flow and neuronal death.^{61,62} Likewise, infection causing inflammatory cascades and impaired flow leads to delirium.^{63,64}

Table 1
Common factors in the development of delirium

Risk Factors	Precipitating Factors
Advanced age	Polypharmacy (≥ 5 medications)
Cognitive impairment, dementia	Psychoactive or sedative medications
Functional impairment, debility	Infection
Sensory impairment, hearing and visual loss	Surgery or trauma
Transient ischemic attack, stroke	Indwelling urinary catheter
Alcohol dependence, abuse	Physical restraints
Major depression	Coma
Comorbidity level, complex multimorbidity	Physiologic/metabolic derangements (abnormal blood urea nitrogen/creatinine, urea, pH, sodium, glucose)

Neurotransmitters such as acetylcholine, serotonin, gamma-aminobutyric acid, and dopamine become imbalanced in delirium, which results in the inability of delirious patients to process information and respond appropriately, as shown in Fig. 3.^{65,66} The result is the clinical manifestation of delirium, an acute confusional state with the inability to hold attention. Thought processes are typically disorganized and the level of consciousness is often affected. As a result, patients are typically either hypervigilant or somnolent, at times appearing almost comatose. Delirium can occur in a mixed state as well, alternating between an agitated, hypervigilant state and a somnolent, hypoalert one. These fluctuations form the types of delirium: hyperactive, hypoactive and mixed.⁶⁷

Older patients accumulate neuronal, dendritic, and microglial damage or even death over time.⁶⁵ They are also more likely to have cerebrovascular disease and a history of head trauma. As a result, older brains seem to be less able to deal with stressors and more likely to develop and have difficulty clearing delirium.

Causes

As mentioned earlier, most cases of delirium result from a complex multifactorial process^{49,65} (Fig. 4). It is important to determine underlying causes contributing to this syndrome since treating these issues is the best way to clear delirium.

Neurologic conditions such as stroke, encephalitis or meningitis, and ischemic or traumatic brain injury are obvious potential causes of delirium. Cardiovascular disorders that impair blood flow and oxygenation are also important causes, including myocardial infarction, heart failure, pulmonary embolism, and shock. Infections can cause delirium with urinary tract infections and pneumonia being the most common among older patients.

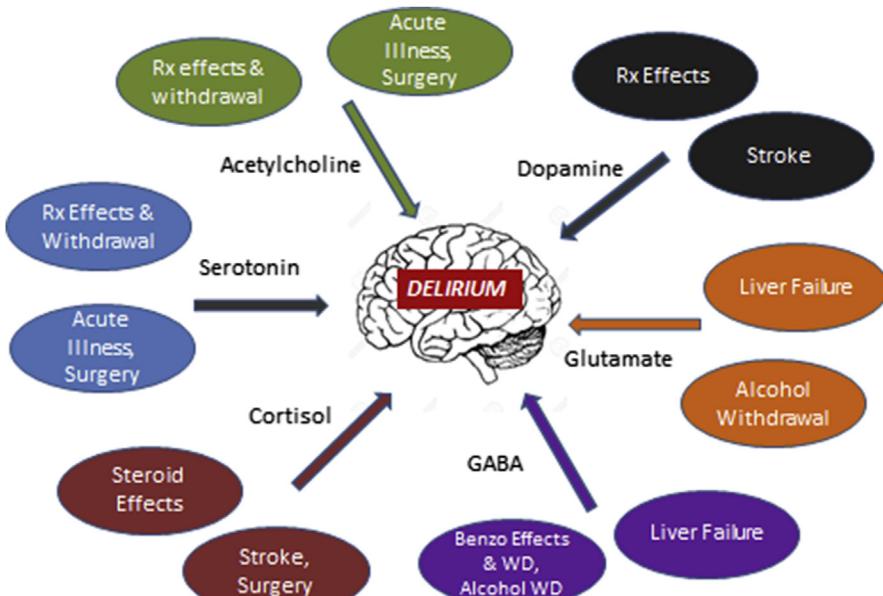


Fig. 3. Neurotransmitter imbalance in delirium. Rx, medication; WD, withdrawal.

Neurological

- Stroke
- Trauma/Subdural hematoma
- Seizure

Endocrine

- Hyperthyroid/hypothyroid

Cardiovascular

- MI, Heart Failure
- Arrhythmias
- PE/DVT
- Shock

Pulmonary

- Hypoxia
- Hypercapnia
- Respiratory distress

Gastrointestinal

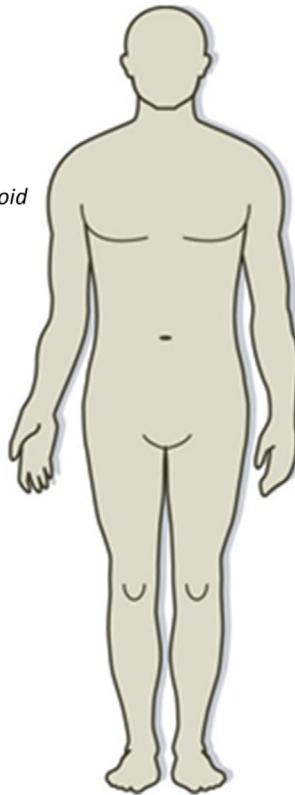
- Constipation
- Impaction

Renal

- Acute renal failure
- Uremia

Urinary

- Retention

**Psychiatric**

- Drug Abuse/Withdrawal

Sensory Impairment

- Hearing & Visual loss

Infections

- Encephalitis, Meningitis
- Pneumonia, Influenza
- Gastroenteritis, Colitis
- UTI
- Prostatitis

Metabolic Derangements

- Glucose
- Sodium
- Potassium
- pH/acidosis/alkalosis

Medications

- Sedatives/hypnotics
- Antipsychotics
- Anticholinergics
- Antidopaminergics
- Opioids
- Central Relaxants

Fig. 4. Common causes of delirium by system. MI, myocardial infarction; PE/DVT, pulmonary embolism/deep vein thrombosis; UTI, urinary tract infection.

Age related changes predispose older adults to have difficulty emptying the bladder and rectum. Sarcopenia, the systemic loss of skeletal and smooth muscle that occurs with more advanced aging, contributes to these disorders, making urinary retention and constipation/impaction common causes of delirium in this population.

Pain is another cause of delirium that practitioners do not want to miss. Uncontrolled pain causes significant distress and, if untreated, can result in delirium. Detecting pain among elderly patients can be more difficult because of sensory loss, communication difficulties, stoicism and dementia. Cognitively impaired patients must be especially watched for nonverbal signs of pain because they cannot reliably report their pain symptoms.

Medication side effects and toxins, including heavy metals, can also cause delirium.^{51,55} Although almost any medication or herbal remedy can cause delirium, some drug classes have been clearly shown to be more likely to do so. These drugs include anticholinergic medications, antidopaminergics, antipsychotics, hypnotics, and sedatives, as well as other centrally acting drugs.⁵²⁻⁵⁵ Medications have been assessed through a variety of ways to assist clinicians in gauging which medications are less likely to cause confusion in elderly or at-risk patients, such as the Beers criteria⁶⁸ and the Anticholinergic Burden Score.^{69,70} Some common medications known to cause delirium are listed in **Table 2**. Note that herbs and over-the-counter medications.

Frailty, a condition of physiologic homeostenosis, commonly occurs in elderly patients and may predispose them to develop confusion when imbalances such as those noted earlier occur.⁷¹ Younger adult patients with significant multimorbidity respond physiologically as much older patients would and therefore should be considered at increased risk for delirium as well.

Differentiation from Dementia

It is important, and at times difficult, to discern dementia behaviors from delirium, especially Lewy body dementia, which can have alterations in attention as part of its symptom profile. The key to differentiating whether a patient is experiencing dementia-related behaviors or acute brain failure is in a combination of history taking and determination of attention.

Many patients with dementia have behavioral disturbances, also often referred to as psychosis, and may have hallucinations and other cognitive disturbances. However, with the exception of some patients with Lewy body dementia, patients with dementia should not have a disturbance of attention.⁴⁸ In effect, unless the dementia is end stage, patients should be able to have a conversation and perform some tests of attention such as counting backward from 20 or naming the months of the year or days of the week in reverse. Patients' abilities to perform these tests vary based on the level of cognitive decline, but each patient should be able to show some level of attention. This observation is important, along with documenting a change from the patient's normal baseline status (obtained from collateral history obtained from family or caregivers), in determining whether an acute change indicates that delirium has occurred. This finding helps clinicians differentiate dementia from delirium.

TREATMENT

Delirium treatment should focus on addressing the underlying cause (**Fig. 5**). Treating the cause for brain failure is the only way to achieve clearing of delirium. Many studies have attempted to address prevention as well as treatment of behavioral disturbances, including agitation, that can be associated with delirium.

Identification of at-risk populations of patients should be part of hospital admissions as well as provider assessments in all care areas. The following precipitating factors

Table 2
Common medications that cause delirium

Drug Class	Example Medications
Anticholinergics	Diphenhydramine, promethazine, oxybutynin
Antidopaminergics	Metocloperamide, chlorpromazine, bupropion
Sedative/hypnotics	Benzodiazepines: diazepam, clonazepam Barbiturates: secobarbital, phenobarbital Hypnotics: zolpidem, zaleplon, ramelteon
Antipsychotics	Haloperidol, quetiapine, olanzapine, ziprasidone
Opioids	Hydrocodone, oxycodone, morphine
Other centrally acting agents	Relaxants: tizanidine, cyclobenzaprine, baclofen Dopaminergic: carbidopa/levodopa, selegiline Stimulants: amphetamine, methylphenidate

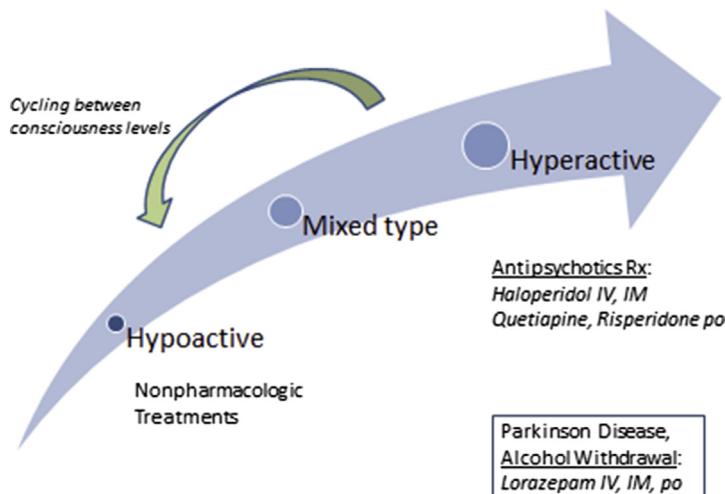


Fig. 5. Delirium treatment by type. IM, intramuscular; IV, intravenous; po, by mouth.

should be considered when assessing for delirium risk: cognitive impairment and disorientation, dehydration, hypoxia, immobility, infection, polypharmacy, pain, malnutrition, sensory impairment, and sleep disturbance.⁷² Education of health care providers on the recognition of risks and symptoms of delirium has been shown to reduce the prevalence.^{73–78}

Treatment guidelines for both hyperactive and hypoactive delirium recommend avoidance of medications, including sedatives and antipsychotics, in favor of nonpharmacologic interventions because there is no clear evidence for the use of these medications in delirium.^{47,79,80} Supportive care by family members and nursing should focus on close, continuing observation.^{81,82} Reassuring patients that they are safe, and reorientating them to place, people, and plans are also helpful.⁴⁷ Pharmacologic interventions should be reserved for the management of persistent behavioral symptoms that do not respond to nonpharmacologic treatments and place the patient at risk for harming themselves or others.^{81,83–86}

Many practitioners still use antipsychotic medications for both hyperactive and hypoactive delirium despite the lack of clear evidence to support their use.⁸⁵ Haloperidol has long been considered the gold standard medication for the treatment of persistent agitated behaviors not responsive to nonpharmacologic interventions. It remains the most commonly used medication despite waning evidence for its efficacy in either prevention or treatment of delirium.^{84,85}

More recently, newer second-generation antipsychotics such as quetiapine, risperidone, and olanzapine have been used for short-term treatment in patients who are able and/or agreeable to take oral medications. However, olanzapine is the only one to be included in prior recommendations.⁸³ When these medications are used, practitioners should be cautioned to ensure that corrected QT (QTc) (per 12-lead electrocardiogram) is not prolonged because antipsychotic medications are known to cause prolongation. In addition, a thorough medication review should be done to ensure there are no potential drug interactions or other medications that might contribute to prolongation of the QTc.^{83,87}

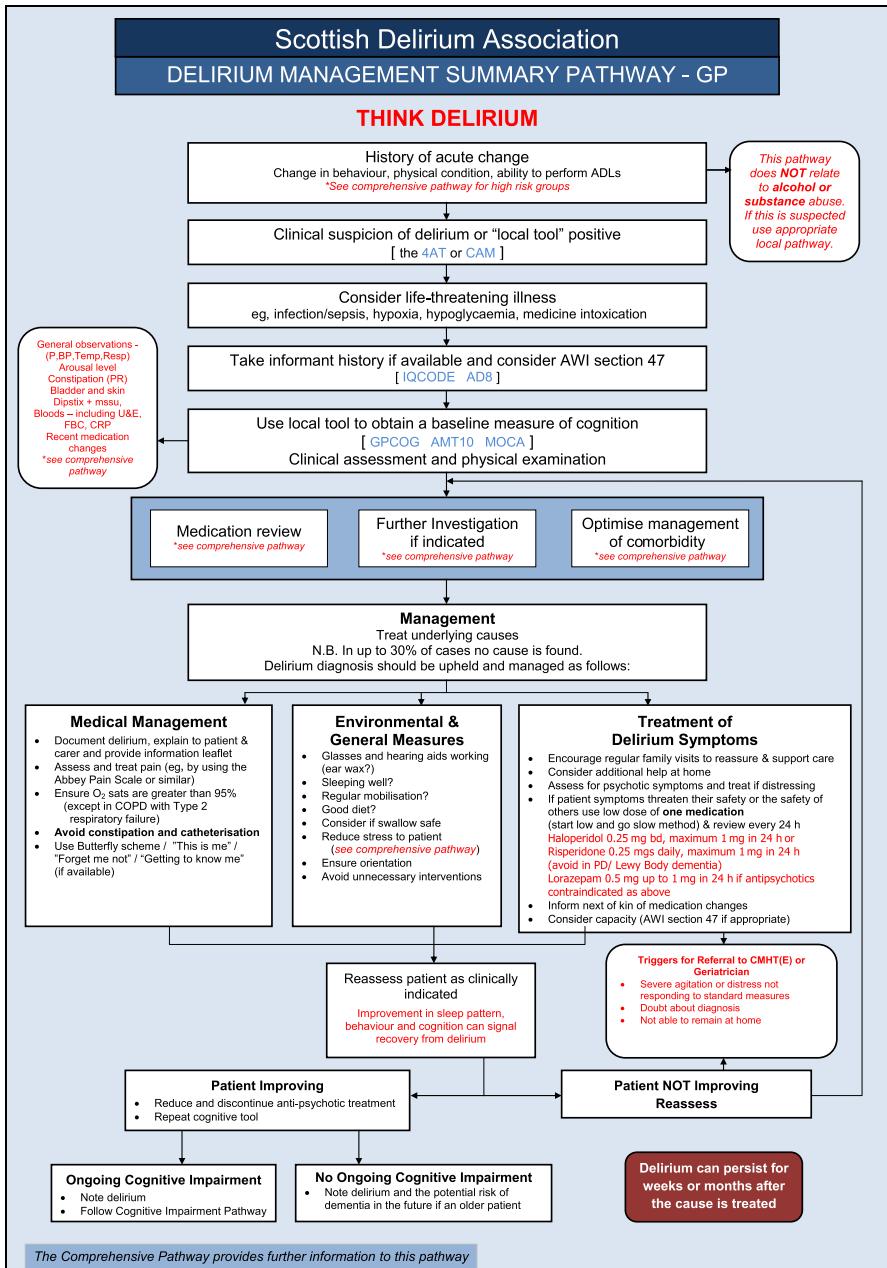


Fig. 6. Scottish Delirium Association delirium management summary pathway. ADLs, activities of daily living; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GP, general practitioner; P, pulse; Resp, respiration; Temp, temperature. (From Scottish Delirium Association. Available at: <http://www.scottishdeliriumassociation.com/>. Accessed February 10, 2017; with permission.)

In general, benzodiazepine medication should be avoided for most patients because these medications can worsen delirium.⁸⁸ For some patients who have persistent, resistant symptoms, or specialized groups such as patients experiencing alcohol or benzodiazepine withdrawal or patients with Parkinson disease, these medications may be used at the discretion of the practitioner and assuming that the risks are outweighed by potential benefits of the medication. As with all medication dosing in the elderly, benzodiazepine and antipsychotic doses should be low and initiated cautiously.

Guideline flow charts such as those published by the Scottish Delirium Society (scottishdelirium.com) help simplify the complexity of addressing delirium assessment and treatment. The chart for general practitioners is shown in Fig. 6. Additional guidelines for nursing homes and a more comprehensive guideline can be found in Appendices 2 and 3.

SUMMARY

Although delirium remains primarily an acute-care issue, its importance cannot be overestimated for primary care, outpatient specialty, postacute care, and long-term care providers. With the continued aging of the world population, dementia, and with it delirium, will continue to be common health problems. Prompt identification of delirium and its differentiation from dementia will be important to quickly discern necessary treatment in the outpatient setting. This distinction includes knowing when to refer patients for emergency or inpatient care. Likewise, learning to identify prolonged or subacute delirium in patients recently hospitalized will be important for outpatient providers. As research continues in delirium, providers will be able to better avoid precipitating factors such as offending medications while providing more specific treatments to clear this important geriatric syndrome.

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APPENDIX 1: 4-AT DELIRIUM ASSESSMENT

**Assessment test
for delirium &
cognitive impairment**Patient name: *(label)*

Date of birth:

Patient number:

Date:

Time:

Tester:

CIRCLE**[1] ALERTNESS**

This includes patients who may be markedly drowsy (eg, difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	0
Mild sleepiness for <10 s after waking, then normal	0
Clearly abnormal	4

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	0
1 mistake	1
2 or more mistakes/untestable	2

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December." To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 mo or more correctly	0
	Starts but scores <7 mo/ refuses to start	1
	Untestable (cannot start because unwell, drowsy, inattentive)	2

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg, paranoia, hallucinations) arising over the last 2 wk and still evident in last 24 h

No	0
Yes	4

4 or above: possible delirium +/- cognitive impairment

1–3: possible cognitive impairment

0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE

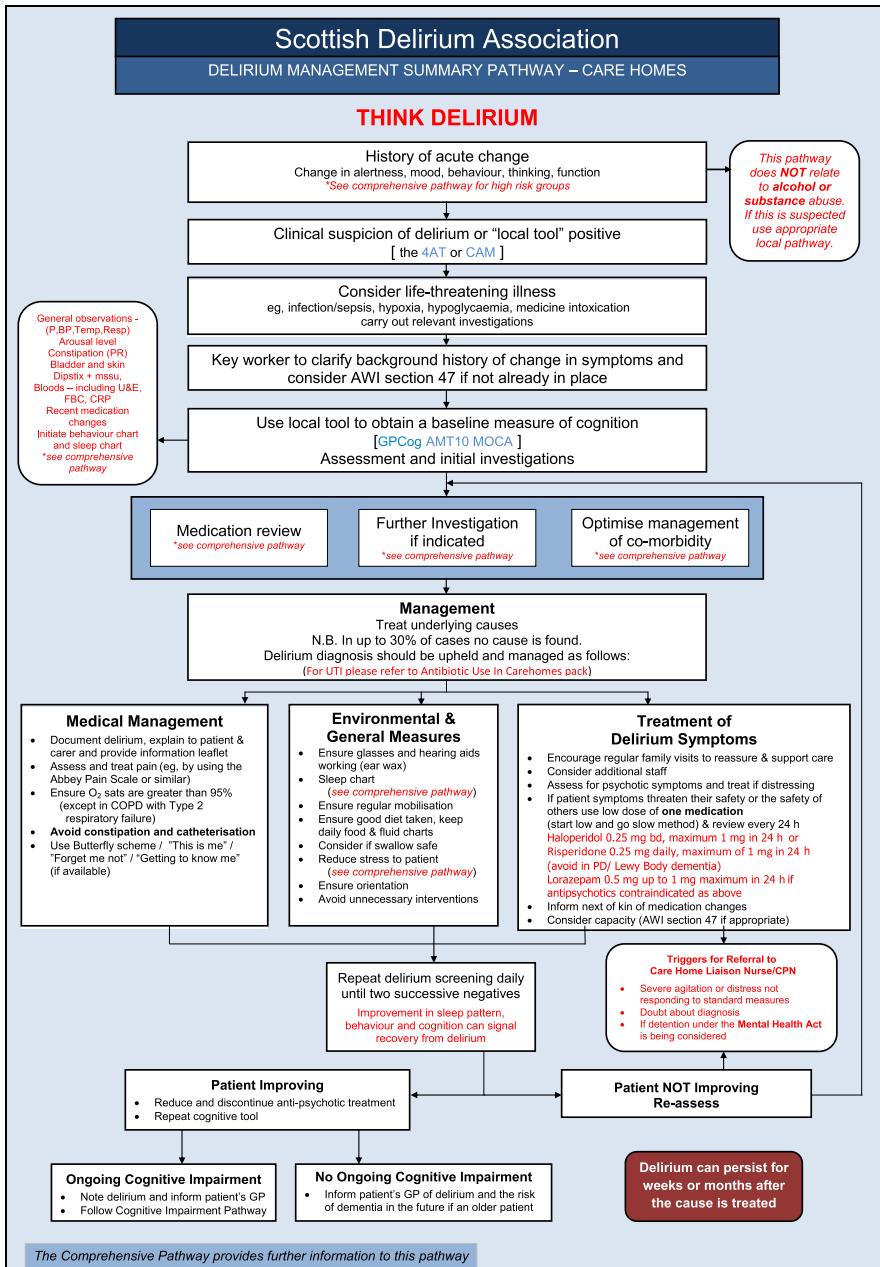
GUIDANCE NOTES

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more suggests delirium but is not diagnostic; more detailed assessment of mental status may be required to reach a diagnosis. A score of 1–3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment; more detailed testing may be required depending on the clinical context. Items 1–3 are rated solely on observation of the patient at the time of assessment. Item 4 requires information from one or more source(s), eg, your own knowledge of the patient, other staff who know the patient (eg, ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, "Are you concerned about anything going on here?"; "Do you feel frightened by anything or anyone?"; "Have you been seeing or hearing anything unusual?"

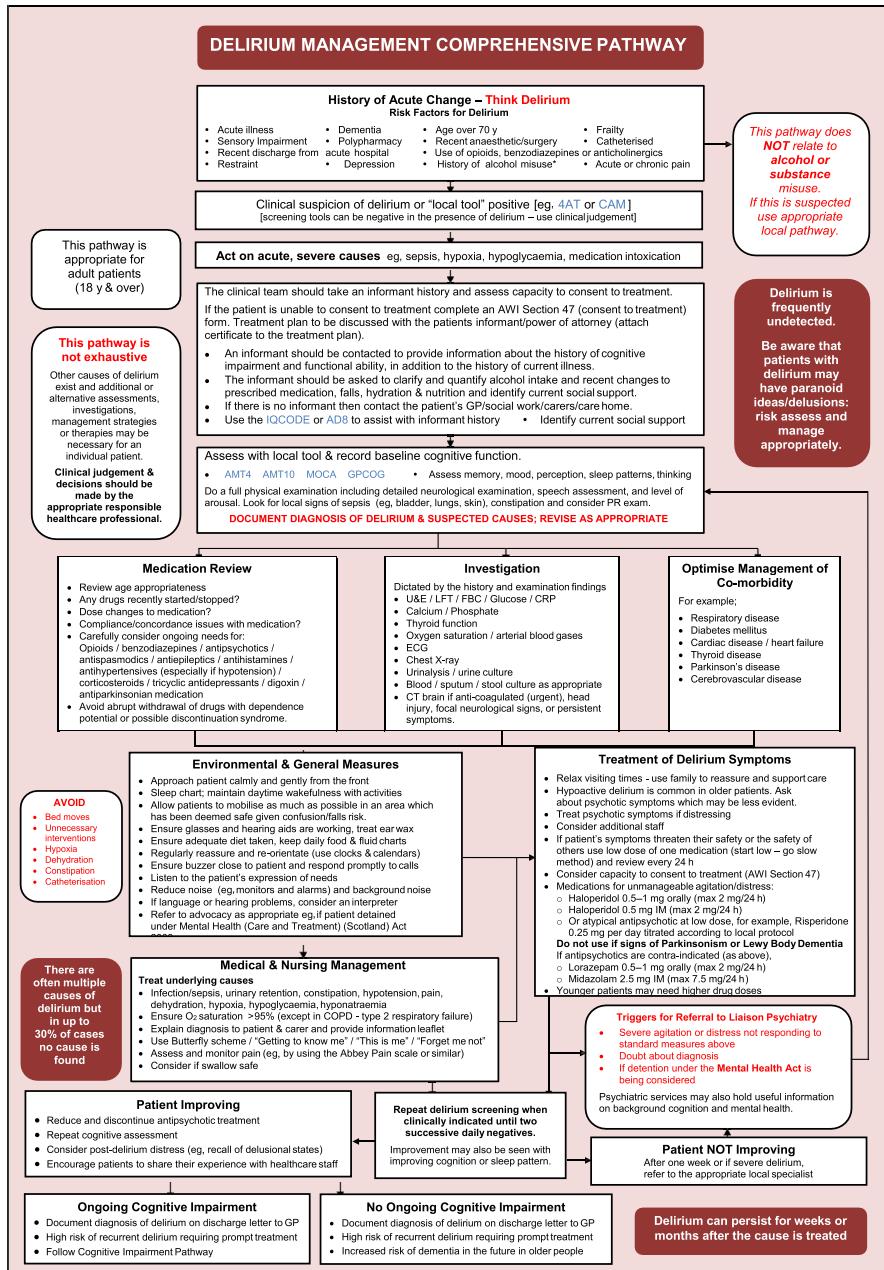
Version 1.2. Information and download: www.the4AT.com

APPENDIX 2: SCOTTISH DELIRIUM ASSOCIATION DELIRIUM MANAGEMENT PATHWAY FOR CARE HOMES



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APPENDIX 3: SCOTTISH DELIRIUM ASSOCIATION COMPREHENSIVE DELIRIUM PATHWAY



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