CLINICAL PRACTICE GUIDELINES

Delirium in adult cancer patients: ESMO Clinical Practice Guidelines[†]

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Delirium is a neurocognitive syndrome that commonly occurs in older populations and people with cancer, particularly in those with advanced disease and in the last hours or days of life. While an underlying malignancy and its complications predispose a person to develop delirium, many of the treatments used in the management of cancer also increase the risk of delirium [1]. In addition to being associated with an increased risk of mortality and causing significant physical morbidity, delirium is often a severely distressing experience, not only for patients, but also for families and professional caregivers [1].

The target population for this European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) is adults with cancer who are at risk of delirium or have been diagnosed with delirium. The intended users for this CPG are healthcare professionals working in the field of oncology, in order to inform both clinical decisions and standards of care.

Incidence and epidemiology

The incidence of delirium in advanced cancer patients has been reported as varying greatly [2], with up to 88% of patients developing delirium in the last weeks to hours of life [3]. This variation depends on the study population, the delirium definition and method of assessment used and staff training, as well as delirium subtype and methods used for subtype classification. In clinical settings, physicians and nurse specialists continue to underdiagnose delirium [4–8]. The hypoactive subtype is not only the most frequent delirium clinical subtype in patients with cancer [9–11] but is also commonly missed by the oncology team [4]. Combining the assessments of palliative care physicians and nurses has been shown to improve the detection of delirium in terminal cancer patients [9].

The majority of studies in oncological populations examine delirium in advanced cancer patients admitted to palliative care units (PCUs) or inpatient palliative care consultation services [4, 9, 12–17] and do not include cancer survivors (see Supplementary Table S1, available at *Annals of Oncology* online). There is limited published information regarding the frequency of delirium in outpatients with advanced cancer [2]. The authors' literature review found one study in an outpatient setting [18]: six out of the 69 (8.6%) patients (aged 33–70 years) with head and neck cancer and receiving outpatient treatment developed delirium, based on assessment with the Confusion Assessment Method (CAM). However, ~45% of their caregivers reported delirium retrospectively as part of a subsequent mixed-methods study. The literature review found one study of 243 patients presenting to an emergency department [10].

The reported prevalence of delirium is dependent on the patient setting: ~10% of advanced cancer patients presenting to an emergency department [8], 43% on admission to a general medical

ward [10] and up to 42% on admission to a PCU [12, 17]. During hospitalisation, 16.5% [19] to 18% [20] of patients with cancer or a haematological malignancy admitted to oncology or internal medicine units developed delirium and 26%–47% developed it after admission to an acute PCU (APCU) [9, 12, 13, 15, 17]. Most studies confirm that the frequency of delirium increases with age [5, 9, 20]. At the end of life, ∼90% of patients who died in an APCU had delirium [12] (Supplementary Table S1, available at *Annals of Oncology* online, provides more detailed information on the prevalence and incidence of delirium in admitted patients with cancer, and frequency of different delirium subtypes when reported).

Mortality and morbidity

Outcomes of delirium in the general hospital population have been examined in systematic reviews; delirium is associated with increased post-discharge mortality [hazard ratio 2.0; 95% confidence interval (CI): 1.5–2.5] and institutionalisation [odds ratio (OR) 2.4; 95% CI: 1.8–3.3] [21]. Estimates in oncological populations vary widely because samples are drawn from a range of clinical contexts and settings [22]. Nonetheless, associations between delirium and adverse outcomes are evident in patients with cancer to an even greater extent.

Mortality

A number of studies report the association of delirium with mortality (see Supplementary Table S2, available at *Annals of Oncology* online). Mainly conducted in APCUs, all studies except two [23, 24] reported associations between delirium and increased mortality rates of at least twofold. The highest estimate was in a sample undergoing bone marrow transplant (OR 14) [25]. The association is consistent when considering both in-patient and post-discharge mortality. The delirium-mortality association was still observed where crude estimates were adjusted for covariates including age, sex and cancer type. In cancer patients in the last months of life, shorter survival is associated with the hypoactive and mixed delirium subtypes [26].

Prognostic tools for predicting survival in terminally ill cancer patients, such as the Palliative Prognostic Index (PPI) and In-hospital Mortality Prediction in Advanced Cancer Patients (IMPACT) model, include delirium as a variable [27, 28]. The Palliative Prognostic (PaP) score was recently updated with the incorporation of delirium (D-PaP score) as a significant variable in predicting survival [29].

Morbidity

There are wider effects on general health as a consequence of delirium, though this has not been studied systematically in oncology populations. Extrapolating from older people (aged ≥ 65 years) admitted to a hospital rehabilitation unit, delirium increases rehabilitation needs [30] and may be complicated by pressure sores and aspiration pneumonia [31] and significantly higher rates of residential or nursing home placement in the 2 years following admission [32]. Other studies have shown that functional decline is more common following delirium [33–35], along with higher rates of readmission [36]. Overall, these

associations are more pronounced in patients with underlying dementia [37]. In patients admitted to an APCU, more severe delirium is associated with lower performance status, greater symptom burden and longer length of stay [15]. Delirium also causes significant psychological distress for patients, their families and healthcare providers [1]. (See also the section on the 'Experiential impact of delirium' for further discussion of this topic.)

Risk factors

Risk factors for delirium are often described as 'predisposing' or 'precipitating'. 'Predisposing' factors refers to those conditions that already exist in a person at baseline, and increase the person's susceptibility to develop delirium, whereas 'precipitating' factors are those that are responsible for activating a specific delirium episode. Direct and indirect risk factors and other predisposing comorbidities for delirium in the cancer patient are summarised in Table 1. As delirium is ubiquitous, it is possible that cancer survivors with no active disease but who have developed cognitive impairment due to the effects of cancer and/or its treatment may also be at risk for developing delirium. None of the papers that were reviewed for the epidemiology section (see Supplementary Table S1, available at *Annals of Oncology* online) reported on cancer survivors.

Studies in oncology settings have not documented specific socio-demographic and disease-related predictive factors for delirium. In addition, most studies in cancer patients have explored a range of psychiatric diagnoses rather than addressing factors specific to delirium. As a consequence, the number of patients with delirium in these studies has often been insufficient to precisely determine associated risk factors.

A multifactorial model for hospitalised patients aged ≥ 70 - years has been proposed [5]. The model involves the interaction between 'baseline vulnerability' and 'precipitating factors or insults'. Predisposing factors that are specifically demonstrated to be contributory to the baseline vulnerability in older patients include visual impairment, severity of illness, pre-existing cognitive impairment and dehydration (demonstrated by an elevated blood urea nitrogen/creatinine ratio of ≥ 18). Patients who have high baseline vulnerability may develop delirium with any precipitating factor, whereas those with low baseline vulnerability will be more resistant to the development of delirium, even with noxious insults. Accordingly, in less advanced cancer, relatively minor intercurrent illness can result in delirium in older, frail persons [38], whereas more severe acute illness might be necessary to produce delirium in younger individuals.

In a prospective observational study over a 10-week period, 113 patients (145 hospital admissions) with haematological malignancies or cancer were admitted to an acute oncology unit. The majority of patients (57%) had a haematological malignancy, most commonly lymphoma (*n* = 47). For patients with cancer, the stage was not reported. The five factors associated with the occurrence of delirium on multivariate analysis were found to be: advanced age, cognitive impairment on admission, hypoalbuminaemia, presence of bone metastases (independent of serum calcium level) and the diagnosis of a haematological malignancy [20]. From a retrospective study of 574 patients with solid malignancies and 1733 admissions to a medical oncology ward, Neefjes et al. recently developed

Table 1. Risk factors and predisposing comorbidities implicated in the onset of delirium in adult patients with cancer

Direct risk factors for delirium

Cancer related-factors [20]
Primary CNS tumours
Secondary CNS tumours
– Brain metastases
– Meningeal metastases
Para-neoplastic neurological syndromes

Toxicities from anticancer treatments [20, 39, 48]
Radiation to brain: acute or delayed encephalopathy
Chemotherapy: methotrexate, cisplatin, vincristine, procarbazine, aspara-ginase, cytarabine (cytosine arabinoside), 5-fluorouracil, ifosfamide, tamoxifen (rare), etoposide (high-dose), nitrosourea compounds, alky-lating agents (high-dose or arterial route)

Indirect risk factors for delirium

Physical complications in cancer patients [40, 41]
Metabolic encephalopathy due to hepatic, renal or pulmonary failure
Electrolyte abnormalities, including SIADH
Glucose abnormalities
Infections, sepsis—at any site, including intravenous lines
Haematological abnormalities
Nutritional deficiency
– Thiamine (vitamin B1)
– Folic acid (vitamin B9)
– Cobalamin (vitamin B12)
Dehydration
Post-seizure; nonconvulsive status epilepticus
Vasculitis

Medications [5, 45]
Anxiolytics, hypnotics
Opioids
Corticosteroids
NSAIDs
Anticonvulsants
Anticholinergics
– Scopolamine (hyoscine hydrobromide)
– Atropine
– Belladonna alkaloids
– Drugs with established anticholinergic activity, e.g. tricyclic antidepressants, diphenhydramine, promethazine, trihexyphenidyl, hyoscine butylbromide
Other psychoactive: antipsychotics, antidepressants, levodopa, lithium
Anti-infectives: ciprofloxacin, acyclovir, ganciclovir
Histamine H2 blockers
Omeprazole
Immunomodulators: interferon, interleukins, ciclosporin
Medication polypharmacy

Other status or predisposing comorbidities [5, 39]
Age > 70 years
Pre-existing cognitive impairment, e.g. dementia
History of delirium
Hearing impairment

Continued

Table 1. *Continued*

Indirect risk factors for delirium

Other status or predisposing comorbidities [5, 39]
Visual impairment
Urinary retention or use of urinary catheter
Constipation
Alcohol or drug abuse, or withdrawal (including nicotine)
CNS diseases or trauma; history of stroke or transient ischaemia
Liver failure
Renal failure
End-stage cardiac disease
End-stage lung disease
Endocrinopathy

CNS, central nervous system; NSAID, non-steroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

a delirium prediction algorithm [39]. They identified that patients admitted as an emergency in combination with a metabolic disturbance had a one in three delirium risk. Cancer stage was not recorded, except for the presence of intracranial disease (as primary tumour or metastasis) in 36 patients (6%). Study limitations include a low overall incidence of delirium (3.5 per 100 admissions) and retrospective design. Other delirium risk factors have been implicated in other studies, including age, dementia, depression, alcohol abuse, poor functional status, organ dysfunction and abnormal levels of serum sodium, potassium or glucose, among others [40–44]. Moreover, many medications are implicated as risk factors for delirium, in particular opioids, benzodiazepines, corticosteroids and antipsychotics [45] (Table 1). In a study of 140 hospitalised, confused adult cancer patients, 31% had a single determinant factor for their delirium, whereas 69% had multiple factors, with a median of three probable causes [46]. One-hundred and two patients (73%) were known to have metastatic cancer, with brain or leptomeningeal metastases present in 36 patients (25%). Contributory precipitants of delirium included: medications (predominantly opioids) in 64% of patients, electrolyte disturbance in 46% and infections in 46% [46]. These cited factors may be considered as indirect risk factors in the multifactorial aetiology of cancer-related delirium (Table 1).

Considering direct tumour effects, cognitive compromise is often one of the most common presentations of brain and leptomeningeal metastases [47]. Para-neoplastic encephalitis, which can be associated with anti-neuronal antibodies (such as anti-Hu and others), is a potential rare cause of delirium [47]. With respect to direct effects of cancer-specific treatments, varying levels of cognitive impairment have been reported in association with treatment with both chemotherapy and radiotherapy [48–51] (Table 1).

The distinction between predisposing and precipitating factors for delirium in advanced-stage cancer becomes somewhat more arbitrary than in earlier stages of the disease as a result of the multifactorial aetiology of delirium and the overall comorbidity burden [12, 20]. Nonetheless, in analysing the causes of delirium, it is important to recognise that many precipitating risk factors are common and potentially reversible in patients with advanced malignant disease.

Table 2. Clinical features of delirium[a] (derived from [55, 58, 69, 171–174])	
Prodromal features (often single symptoms)	e.g. anxiety, restlessness, irritability, disorientation, sleep disturbances
Cognitive disturbance	e.g. impaired attention and awareness (with a change from baseline), impairment of consciousness, disturbance in level of arousal, disorientation to environment (time, place) or self (person), reduced concentration, disorganised thought process, impaired immediate recall and recent memory, visuospatial dysfunction, language disturbance, incoherent speech
Perceptual disturbance and delusions	Examples of perceptual disturbances: hallucinations (usually visual or tactile), illusions, misinterpretations — Delusions that tend to be transient in nature
Psychomotor disturbance	— Hypoactive delirium: reduced psychomotor activity with reduced movement, lethargic, decreased flow of speech — Hyperactive delirium: increased psychomotor activity with agitation, restlessness, increased flow of speech, enhanced startle reaction — Mixed delirium: unpredictable, fluctuating features of both hypoactive and hyperactive delirium
Sleep–wake cycle disturbance	e.g. insomnia, distressing dreams and nightmares, reversal of sleep–wake cycle, nocturnal worsening of symptoms, excessive daytime somnolence
Emotional disturbance	e.g. anxiety, fear, irritability, emotional lability, euphoria, depression, apathy, withdrawal (Person with delirium may call out, scream or moan)
Neurological abnormality	e.g. asterixis, tremor, myoclonus, frontal release signs (palmomental, snout, grasp reflexes), dysgraphia, constructional apraxia, dysnomic aphasia
Timeline	— Usually rapid development, over a period of hours to a few days — Fluctuation of severity during a 24-h period, often increasing in the evening and night time — Lasting around 1 week in hospitalised patients[b] (excluding actively dying patients)

[a]Specific diagnostic criteria are codified by the Diagnostic and Statistical Manual of Mental Disorders (DSM) [55] and International Classification of Diseases (ICD) [58] classification systems.
[b]This is dependent on the reversibility of precipitating factor(s), and thus can vary. Symptoms can persist, particularly in older patients.

Clinical assessment, diagnosis and screening

In many patient settings, delirium is often missed [5], in part due to fluctuation of symptoms and hypoactive presentation, and also due to misdiagnosis as another psychiatric disorder. In older people, the diagnosis of delirium superimposed on a pre-existing dementia is particularly challenging. The clinical features of delirium are shown in Table 2. Despite its prevalence in patients with cancer, delirium is frequently not recognised by the primary team in inpatient oncology units [4, 52] and may be misdiagnosed by oncologists in up to 37% of their patients [53].

A number of strategies to improve delirium recognition have been suggested, including the use of diagnostic tools and the introduction of routine screening and severity monitoring. For all patient settings, obtaining a collateral history from family members is often invaluable, along with use of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)—short form [54] where indicated (see Figure 1). This section reports the current evidence on the clinical assessment, diagnosis and screening of delirium in patients with cancer, in addition to the monitoring of delirium severity.

Using validated tools to make a diagnosis of delirium in cancer patients

The reference standard for the diagnosis of delirium is a careful clinical assessment of the patient using Diagnostic and Statistical Manual of Mental Disorders (DSM) [55–57] or International Classification of Diseases (ICD) [58] criteria. This takes time and requires expertise and training. The current version of the DSM criteria, DSM-5, was published in 2013 as the 5th edition and specifies a disturbance in attention and awareness as an essential diagnostic feature of delirium [55] (The ICD-11 revised version is expected to be published in 2018).

Although a variety of tools have been developed to help clinicians make an accurate diagnosis of delirium, few validation studies have been carried out in representative populations of people with cancer or have included sufficient medical diagnostic detail to allow a determination of whether people with cancer were included in the study (see Supplementary Tables S3 and S4, available at *Annals of Oncology* online).

The CAM is a copyrighted instrument and one of the most widely used diagnostic instruments for clinical and research purposes with proven psychometric properties [59]. The CAM was
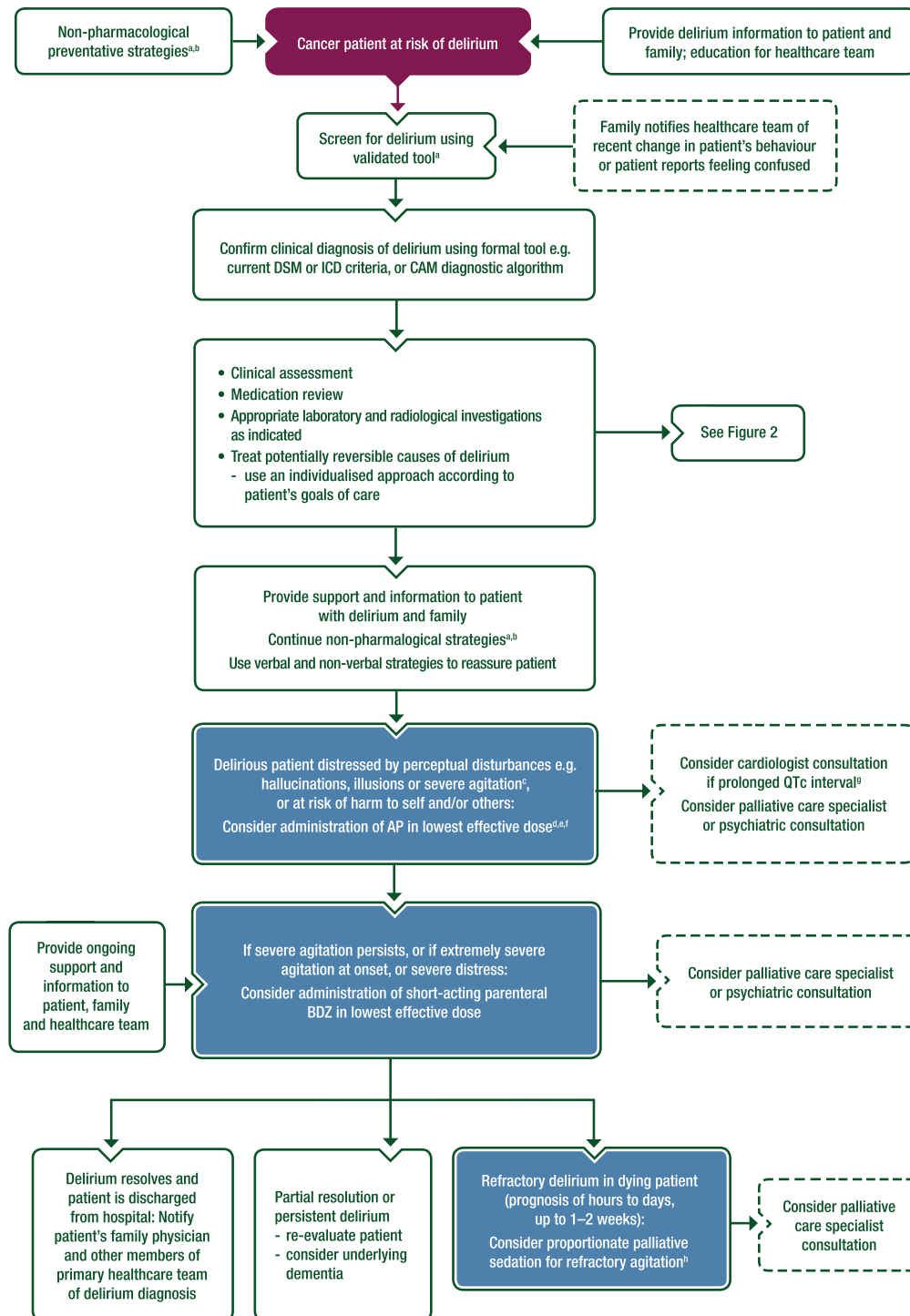
Figure 1. Assessment and management strategy of delirium in adults (18 years or older) with cancer.
[a]Insufficient evidence of benefit/harm in this patient population.
[b]See Table 3.
[c]Clinical re-evaluation of patient to exclude other causes of agitation, e.g. unrelieved pain, full bladder.
[d]Avoid AP or use with caution in patients with Parkinson's disease or dementia with Lewy bodies.
[e]Monitor for effectiveness of AP in reducing patient distress and delirium symptoms.
[f]Monitor for adverse effects of AP, e.g. EPSEs (including dystonia, akathisia and parkinsonism).
[g]Increased risk of torsade de pointes, ventricular fibrillation and sudden cardiac death if QTc interval > 500 ms or an increase of ≥ 60 ms from baseline.
[h]Refer to ESMO Palliative Sedation CPG [168].
AP, antipsychotic; BDZ, benzodiazepine; CAM, Confusion Assessment Method; CPG, Clinical Practice Guideline; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPSE, extrapyramidal side effect; ESMO, European Society for Medical Oncology; ICD, International Classification of Diseases; QTc interval, rate-corrected QT interval.

Table 3. Strategies used in multicomponent non-pharmacological interventions[a] for the prevention and management of delirium in older hospitalised non-ICU patients [5, 69, 175]

Targeted patient-related risk factors for delirium	Strategy
Cognitive impairment	Reorientation of patient by staff and family
	Explain where they are, who they are, who you are, and your role
	Use orientation white board, visible clock
	Use cognitive stimulating activities, e.g. reminiscence
	Avoid frequent room changes
Visual impairment	Use eyeglasses and other visual aids
Hearing impairment	Use hearing aids or other portable amplifying devices
	Ensure ears are free of impacted wax
Immobility	Encourage active range-of-motion exercises for all patients
	Encourage mobilisation as allowed by patient's performance status, providing walking aids if needed
	Avoid unnecessary urinary catheterisation
	Avoid using physical restraints
Dehydration	Encourage patient to drink, provided they can swallow safely
	Assist patient at mealtimes if necessary
Sleep–wake circadian cycle disturbance	Daytime: increase exposure to daylight whenever possible, discourage napping during the day
	Evening: warm, non-caffeinated drinks, relaxing music at bedtime, minimise light, noise and disruptions during the night

[a]Interventions include person-centred, tailored and coordinated, multidisciplinary team approaches to care. At this time, there is limited research evidence for these interventions for the prevention and management of delirium in patients with cancer.
ICU, intensive care unit.

developed and validated against reference standard ratings of geriatric psychiatrists that were based on the DSM Third Edition Revised (DSM-III-R) criteria. The CAM diagnostic algorithm is based on four cardinal features of delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganised thinking and (4) altered level of consciousness. A diagnosis of delirium according to the CAM algorithm requires the presence of features (1), (2) and either (3) or (4). As part of the assessment, trained healthcare staff should also administer a brief test of cognition, such as the Short Orientation Memory Concentration Test (SOMCT) [60] and attention [for example, to ask the patient to recite the months of the year backwards (MOTYB)]. The CAM training manual for the 'short' CAM version was developed to facilitate appropriate use of the instrument and is available online [61], as is the training manual for the comprehensive 'long' CAM version.

Shi et al. conducted a systematic review and meta-analysis of diagnostic accuracy in all populations and found that the sensitivity of pooled CAM data was 82% (95% CI: 69%–91%) and the specificity was 99% (95% CI: 87%–100%) [62]. Nevertheless, our search identified only one paper in which the study population described the inclusion of more than 50% of patients with cancer [63]. In this study, the sensitivity was 0.88 (CI: 0.62–0.98) and the specificity was 1.0 (CI: 0.88–1.0). It should be noted that this study is at risk of spectrum bias because participants were inpatients at a PCU and are not representative of the entire cancer population.

Recommendation:
- The diagnosis of delirium should be made by a trained and competent healthcare professional using a clinical assessment based on DSM or ICD criteria [III, C].

○ The evidence is insufficient to recommend for or against the routine use of diagnostic tools in making a diagnosis of delirium in cancer patients.

Using validated tools to screen for delirium in cancer patients

A variety of screening tools for delirium have been developed. Few validation studies have either been carried out in populations of people with cancer or have included sufficient medical diagnostic detail to allow a determination of whether people with cancer were included in the study. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) guidelines [64] were employed to assess the study quality of the five studies identified from our systematic literature review [52, 65–68] (see Supplementary Tables S3 and S4, available at *Annals of Oncology* online). All studies are vulnerable to bias due to spectrum or review bias or use of an inappropriate reference standard.

Recommendations:
- The evidence is insufficient to recommend the routine use of screening tools in making a diagnosis of delirium in cancer patients [III, C].
  ○ No randomised controlled trials (RCTs) for screening for delirium in patients with cancer were identified and so there is no direct evidence that screening for delirium is beneficial or harmful in this patient population.
  ○ While screening potentially offers benefits, universal screening may also pose harms, such as misclassification,

subsequent treatment of non-delirious patients or failure to accurately identify or intervene in delirious patients.
- ○ However, given the high incidence of delirium in patients with cancer and its associated morbidity and mortality, we recommend that people with cancer who present to hospital should be observed, at least daily, for recent changes or fluctuations in cognitive or physical function or behaviour (Table 2). For example, sentinel changes for patients in all clinical settings (inpatient, community and ambulatory) may include the following: impaired concentration, slow responses, withdrawal, sleep disturbances, hallucinations, confusion, agitation, restlessness or mood changes [69].
- If any changes in cognitive or emotional behaviour or psychomotor activity suggestive of delirium are present, a trained healthcare professional with expertise in evaluating delirium should carry out a clinical assessment to confirm the diagnosis of delirium [III, C].

Using validated tools to routinely rate delirium severity in cancer patients

The literature search identified three studies utilising the Memorial Delirium Assessment Scale (MDAS) and Delirium Rating Scale (DRS) in the assessment of delirium severity in cancer patients [12, 70, 71] (see Supplementary Table S3, available at *Annals of Oncology* online).

Recommendation:
- The evidence is insufficient to recommend for or against the routine use of tools to assess delirium severity in daily practice [III, C].
  - ○ No RCTs studying the use of validated delirium severity assessment tools in cancer patients were found to demonstrate whether their use is beneficial or harmful.

Management of potentially reversible causes of the delirium episode

Initial evaluation of precipitating risk factors

The rapid detection of delirium and potential risk factors through an appropriate clinical assessment is essential, as studies in patients with advanced cancer show that 20%–50% of delirium episodes can be reversed [12, 16, 72–74] in patients who are not imminently dying (last hours of life). Medication-induced delirium is usually reversible, whereas hypoxic encephalopathy and organ failure are associated with non-reversibility [12, 73, 75].

The delirious patient's capacity to make decisions regarding treatment should be assessed. A functional approach to assessment of capacity should be employed, whereby capacity is regarded as issue-specific and time-specific. While capacity is often impaired (and not infrequently absent), the fluctuating nature of delirium means that patients may experience periods of lucidity during delirium episodes. As a general principle, efforts should be made to maximise an individual's capacity wherever possible. Thus, during periods of relative lucidity, delirious patients should be supported to engage in decision making.

Depending on the current legislation of an individual country, if a patient is assessed as being unable to engage in decision making about their treatment plan, healthcare staff should determine whether the patient has a pre-existing advance care directive. If valid and applicable, then the advance care directive document should be used to guide decision making. However, with the onset of delirium in a patient with advanced cancer, it is also critically important that a patient's preferences for treatments are discussed again after provision of information regarding potential precipitating factors, likelihood of reversal and outcomes. If an advance care directive does not exist, some legal jurisdictions permit a substitute decision maker (SDM) to engage in decision making on the patient's behalf, with consideration of the patient's preferences or values regarding treatments. If the patient had previously expressed wishes for no further intervention and treatment, the focus would be solely on symptomatic management of delirium symptoms, with no attempt made to reverse an end-of-life delirium.

Recommendation:
- For cancer patients whose assessments indicate delirium, identify the predisposing and precipitating factors through a comprehensive initial assessment [III, A].
  - ○ A comprehensive initial evaluation should be carried out to identify and address the precipitating factors, including obtaining the history with corroboration from family or staff, medication review, physical and neurological examination and specific laboratory tests or imaging, as appropriate to the patient's goals of care.

Figure 2 presents the clinical work-up for identifying potential factors contributing to delirium in cancer patients.

Management of precipitating factors of delirium

A multitude of factors may precipitate delirium in patients with cancer, with a range of one to six precipitating factors for a delirium episode [12] (Table 1). Their investigation and management will be dependent on the specific cause(s) and cancer trajectory, as well as the patient's goals of care with respect to healthcare interventions (Figure 2). The next section covers those precipitating factors that are particularly pertinent to the oncology patient in more detail.

Management of polypharmacy. This is an extremely important component of patient care that is frequently overlooked in the management of delirium. (See paragraph 'Deprescribing' in the section 'Pharmacological interventions for delirium prevention and treatment in adults with cancer' for more discussion of this topic.)

Opioid rotation or switching. The practice strategy of opioid rotation (or switching) is often undertaken if signs of opioid-induced neurotoxicity (OIN) are present, unless the patient is imminently dying [76]. Opioid rotation, where one opioid is substituted for another, may lead to a reduction in the accumulation of neuroexcitatory opioid metabolites from the first opioid while at the same time also improving or maintaining analgesia. However, there remains a lack of high level evidence for this strategy in delirious patients [77]: recent systematic reviews found no RCT evidence for opioid switching in people with delirium [78, 79].

Several studies report efficacy in association with an opioid switch in delirious cancer patients. In a prospective study of 17 delirious
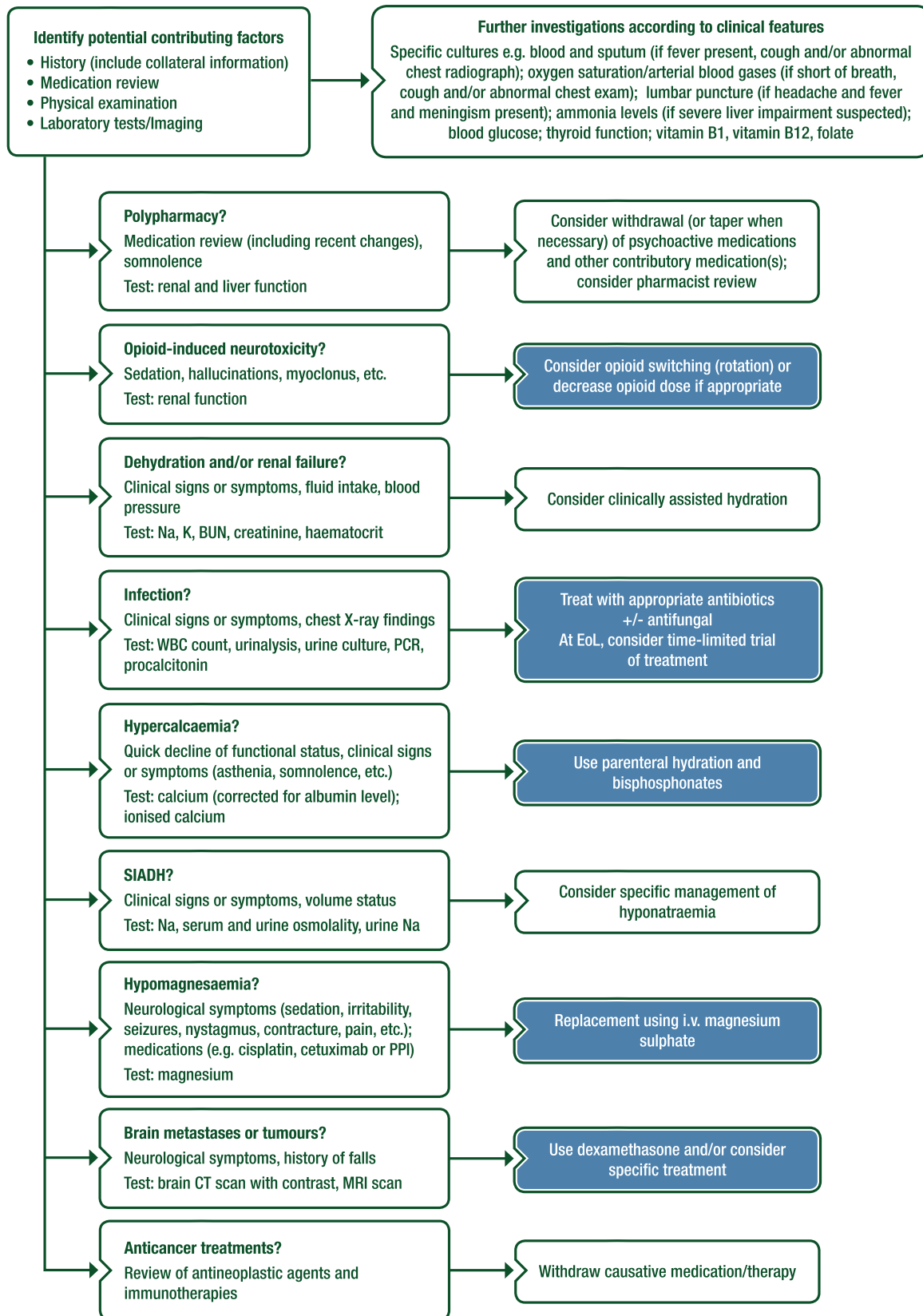
Identify potential contributing factors
- History (include collateral information)
- Medication review
- Physical examination
- Laboratory tests/Imaging

Further investigations according to clinical features

Specific cultures e.g. blood and sputum (if fever present, cough and/or abnormal chest radiograph); oxygen saturation/arterial blood gases (if short of breath, cough and/or abnormal chest exam); lumbar puncture (if headache and fever and meningism present); ammonia levels (if severe liver impairment suspected); blood glucose; thyroid function; vitamin B1, vitamin B12, folate

Polypharmacy?
Medication review (including recent changes), somnolence
Test: renal and liver function

Consider withdrawal (or taper when necessary) of psychoactive medications and other contributory medication(s); consider pharmacist review

Opioid-induced neurotoxicity?
Sedation, hallucinations, myoclonus, etc.
Test: renal function

Consider opioid switching (rotation) or decrease opioid dose if appropriate

Dehydration and/or renal failure?
Clinical signs or symptoms, fluid intake, blood pressure
Test: Na, K, BUN, creatinine, haematocrit

Consider clinically assisted hydration

Infection?
Clinical signs or symptoms, chest X-ray findings
Test: WBC count, urinalysis, urine culture, PCR, procalcitonin

Treat with appropriate antibiotics +/- antifungal
At EoL, consider time-limited trial of treatment

Hypercalcaemia?
Quick decline of functional status, clinical signs or symptoms (asthenia, somnolence, etc.)
Test: calcium (corrected for albumin level); ionised calcium

Use parenteral hydration and bisphosphonates

SIADH?
Clinical signs or symptoms, volume status
Test: Na, serum and urine osmolality, urine Na

Consider specific management of hyponatraemia

Hypomagnesaemia?
Neurological symptoms (sedation, irritability, seizures, nystagmus, contracture, pain, etc.); medications (e.g. cisplatin, cetuximab or PPI)
Test: magnesium

Replacement using i.v. magnesium sulphate

Brain metastases or tumours?
Neurological symptoms, history of falls
Test: brain CT scan with contrast, MRI scan

Use dexamethasone and/or consider specific treatment

Anticancer treatments?
Review of antineoplastic agents and immunotherapies

Withdraw causative medication/therapy

Figure 2. Evaluation* of the adult cancer patient for underlying causes of delirium.
*This should be guided by the patient's goals of care.
BUN, blood urea nitrogen; CT, computed tomography; EoL, end of life; i.v., intravenous; K, potassium; MRI, magnetic resonance imaging; Na, sodium; PCR, polymerase chain reaction; PPI, proton pump inhibitor; SIADH, syndrome of inappropriate antidiuretic hormone secretion; WBC, white blood cell.

patients with cancer, delirium and myoclonus were reversed in 80% and 100% of patients, respectively, after opioid switching from transdermal fentanyl to oral methadone [80]. In another prospective study of 20 cancer patients with morphine-induced delirium who had their opioid treatment rotated from morphine to fentanyl, both delirium symptom scores and pain were significantly reduced [81]. Treatment success was obtained in 13/20 patients on day 3 and 18/20 patients by day 7 [81]. In a prospective study of 20 cancer patients with uncontrolled pain and postulated 'terminal delirium' who underwent opioid rotation to methadone, most patients had at least a short-term improvement in mental status [82].

(See also the section 'Pharmacological interventions for delirium prevention and treatment in adults with cancer' for more discussion of this topic. The reader is also directed to review the ESMO CPG on 'Management of cancer pain in adult patients' for further information [83]).

Recommendation:
- Opioid rotation (or switching) may be appropriate if signs of OIN are present [V, B].
  - A proportion of people develop opioid toxicity, either in association with rapidly increasing doses (especially if their cancer pain is poorly responsive to opioids), with an accumulation of opioid metabolites caused by renal impairment, rapid tolerance or with sensitivity to opioids. One of the effects of opioid toxicity is delirium; therefore, switching opioids (with a reduction in opioid equianalgesic dose by ∼30%–50%) may be useful in alleviating delirium.

Clinically assisted hydration in delirium management. At the present time, there is limited evidence demonstrating the benefit of clinically assisted hydration in the management of delirium. (See also the section 'Non-pharmacological interventions for delirium prevention and treatment in adults with cancer' for evidence regarding hydration and delirium prevention.)

In a multicentre prospective observational study with the primary objective of assessing the quality of life (QoL) of 161 patients with advanced abdominal cancer [74], 4/80 patients (5.3%) who received parenteral hydration of ≥ 1 L/day, as per local guidelines, developed hyperactive delirium (defined as $\geq 2/3$ on the 'psychomotor activity' item of the MDAS) 48 hours before death, compared with 13/56 (17.3%) ($P = 0.009$) receiving < 1 L/day. Of note, patients receiving 'large-volume' hydration developed more bronchial secretions before death [74]. Concerning cancer patients in the last days of life, it is not known whether the systematic hydration of the patient with delirium is beneficial [84].

Recommendation:
- There is limited research evidence for the role of clinically-assisted hydration in the symptomatic management of delirium [V, C].
  - The decision to commence clinically assisted hydration in delirious patients should be made on a case-by-case basis.
  - If in alignment with a patient's preferences and values, and after a considered evaluation of the possible harms and benefits of therapy, clinically assisted hydration may be trialled if dehydration is determined to be a potential precipitating factor for a delirium episode [85, 86].
  - Clinically assisted hydration may also be indicated in somnolent delirious patients who are not drinking, in order to maintain adequate hydration while other clinical interventions are pursued in an attempt to reverse their delirium episode [1].

Management of potentially reversible infections. Infection is a frequent precipitating factor for delirium [73]. Seventy percent of patients with bacteraemia have neurological symptoms ranging from lethargy to coma and $> 80\%$ have abnormalities on electroencephalogram [87, 88]. Although it is common practice to treat the infection associated with delirium, there is no randomised study data to specifically support this practice. In a prospective study of 237 cancer patients admitted to hospice, delirium that was due to an infection and was treated with standard antibiotics had a lower rate of reversibility than delirium related to medications or hypercalcaemia [73].

In delirious patients who are not actively dying from their underlying malignancy and meet the criteria for systemic sepsis, the expert recommendation is that in the absence of an identified source or causative organism, broad-spectrum antibiotics are necessary [89]. The prescribed antibiotics should cover both gram-negative and gram-positive bacteria. A high degree of suspicion for fungal infection as a potential cause of sepsis-associated encephalopathy is also required. Once a causative organism has been identified, narrowing the spectrum of antibiotics is appropriate [89].

Recommendation:
- Infection considered to be a precipitating factor for delirium should be treated, if in accordance with a patient's goals of care and illness trajectory [V, C].
  - An outstanding question is whether a time-limited trial of antibiotics should be undertaken in patients with delirium and no evidence of infection. A prospective cohort study of older medical inpatients with delirium and asymptomatic bacteriuria examined the effect of a test treatment with antibiotics, hypothesising that a urinary tract infection could be responsible for the clinical picture [90]. The older patients treated in this way obtained worse percentages of functional recovery and a higher incidence of *Clostridium difficile* infections, questioning the benefit of a time-limited trial of antibiotics in older patients with delirium and asymptomatic bacteriuria [90].

Hypercalcaemia. Hypercalcaemia should be suspected when a cancer patient experiences acute or subacute confusion, asthenia or drowsiness, even when they are indolent symptoms. Hypercalcaemia-induced delirium is often reversible (in ∼40% of episodes), compared with other underlying causes [73]. However, both hypercalcaemia and delirium are independent negative prognostic factors for survival in cancer patients, with hypercalcaemia often becoming treatment-refractory towards the end of life [91, 92].

Bisphosphonates may efficiently control hypercalcaemia. In two concurrent, parallel, multicentre double-blind RCTs, adult patients with cancer and a corrected serum calcium ≥ 3.00 mmol/L were randomised to receive zoledronic acid in either a 4-mg dose ($n = 86$), or an 8-mg dose ($n = 90$) administered as a 5-minute intravenous (i.v.) infusion or pamidronate (90 mg) as a 2-hour i.v. infusion [93]. i.v. fluids were given before and during the administration of the study drug. Calcium levels normalised in ∼50% of study participants in the zoledronic acid arms,

compared with 33% in the pamidronate arm by day 4. A complete response (defined as attaining a serum calcium corrected for albumin of ≤ 2.70 mmol/L by day 10) occurred in 88.4% of the 4-mg zoledronic acid group, compared with 69.7% in the pamidronate group ($P = 0.002$).

Recommendation:
- Bisphosphonates (such as i.v. pamidronate and zoledronic acid) may control hypercalcaemia and reverse delirium in a substantial number of cases [I, A].
  ○ Parenteral hydration with normal saline not only corrects hypercalcaemia-associated hypovolaemia, but also promotes calciuresis [94].
  ○ If zoledronic acid is used, the 4-mg dose is recommended for the initial treatment of hypercalcaemia, with the 8-mg dose reserved for relapsed or refractory cases [93].
  ○ Denosumab is a human monoclonal antibody and a RANKL (receptor activator of nuclear factor-kappaB ligand) inhibitor. This newer agent is a potent inhibitor of bone resorption used in the management of bone metastases and hypercalcaemia [95]. In an open-label, single-arm, multicentre prospective study of patients with solid tumours or a haematological malignancy and hypercalcaemia refractory to recent i.v. bisphosphonate treatment, subcutaneous (s.c.) denosumab was found to lower serum calcium in 64% (21/33) patients within 10 days [95]. As patients are at increased risk of developing hypocalcaemia after denosumab treatment as compared with zoledronic acid, their calcium level should be monitored post-treatment and calcium and vitamin D supplements started if necessary [96]. It should be noted that denosumab has United States (US) Food and Drug Administration (FDA) approval for the management of hypercalcaemia of malignancy (refractory to bisphosphonate therapy) [97], but does not currently have approval for this indication in Europe by the European Medicines Agency (EMA) (the most recent EMA application was withdrawn from consideration in January 2017 [98]).

Syndrome of inappropriate antidiuretic hormone secretion. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a paraneoplastic endocrine phenomenon is most commonly associated with small cell lung cancer but may also occur with other malignancies [99]. SIADH also occurs with many medications, including chemotherapeutic agents such as platinum-based chemotherapy or vinca alkaloids, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants and antidepressants, as well as in non-malignant pulmonary and neurological illnesses [100]. Patients with SIADH are clinically euvolaemic with inappropriately high urine osmolality and reduced effective serum osmolality [100]. A diagnosis of SIADH should only be made after excluding other potential causes of hyponatraemia such as adrenal insufficiency [100].

Recommendation:
- The discontinuation of implicated medications, fluid restriction and adequate oral salt intake is recommended for the management of confirmed SIADH [V, C].
  ○ In patients with a short prognosis, strict fluid restriction may not be appropriate especially if not in keeping with their goals of care with respect to healthcare interventions.

○ Vasopressin receptor antagonists, such as tolvaptan and conivaptan, have also been used in the management of patients with hyponatraemia due to SIADH. Patients require close monitoring in a hospital setting, as it is important to avoid too rapid correction of severe hyponatraemia due to risk of osmotic demyelination syndrome [101]. Hepatotoxicity has been reported with tolvaptan [101].

Hypomagnesaemia. In advanced cancer patients, certain chemotherapy medications, such as cisplatin or cetuximab, may cause significant hypomagnesaemia [102]. In addition to confusion and hallucinations, other neurological symptoms associated with hypomagnesaemia include irritability, nystagmus, seizures, contractures and severe pain [103]. Replacement using i.v. magnesium sulfate may reverse these symptoms [104].

Recommendation:
- Magnesium replacement is recommended for the management of hypomagnesaemia [V, C].
  ○ Recent attention has been drawn to the importance of monitoring magnesium levels in cancer patients [105].

Anticancer treatments. Many anticancer treatments can cause patient confusion associated with acute encephalopathy. Delirium may occur more frequently with antineoplastic agents that cross the blood brain barrier, such as capecitabine, topotecan or ifosfamide [48, 106]. Most episodes are idiosyncratic and reverse after withdrawal of the offending medication [107]. Novel cancer immunotherapies may cause confusion: the acute release of inflammatory cytokines is thought to lead to the development of neurological symptoms, which usually resolve when the therapeutic agent is stopped [108].

Recommendation:
- Medication or therapy withdrawal is recommended in patients with delirium related to anticancer treatments such as chemotherapy and immunotherapies [V, C].

Non-pharmacological interventions for delirium prevention and treatment in adults with cancer

Non-pharmacological interventions (Table 3) which target delirium risk factors have been recommended for preventing and managing the condition in various clinical practice guidelines, including guidance for the care of inpatients in hospitals [69], residents of long-term care institutions [69] and patients in hospices and other palliative care settings [109, 110]. These have been largely based on expert consensus, although there is now considerable evidence from RCTs that multicomponent non-pharmacological interventions are effective in preventing delirium in hospital inpatients, reducing delirium incidence by around one-third [111]. However, the efficacy and cost-effectiveness of these non-pharmacological strategies (as single and multicomponent interventions) in preventing and treating adult patients with cancer is not clear.

Review of the evidence

From a literature search for RCTs on preventing and treating (or managing) delirium in adults with cancer, one completed study of

non-pharmacological interventions for delirium prevention was found [112] (see Supplementary Figure S1 and Table S5, available at *Annals of Oncology* online). Study quality was appraised using the Cochrane risk of bias tool for appraisal of RCTs, and Revman 5.3 software was used to estimate a mean difference between hydration and control groups for the delirium outcome. In addition, the published protocol for an ongoing feasibility cluster RCT of a clinically assisted hydration intervention in patients with cancer in the last days of life in hospitals and hospices in the United Kingdom (UK) was retrieved [113]. The primary outcome for this trial is prevalent or incident hyperactive delirium assessed using the modified Richmond Agitation-Sedation Scale (RASS).

Bruera et al. [112] evaluated the effectiveness of a daily hydration intervention (1 L of saline administered s.c. over 4 hours at home) compared with placebo (100 mL of saline over 4 hours) to 129 hospice patients with advanced cancer in the US. Study participants were aged 41–92 years, with a median age of 67 years; 47% were female, and there was a diverse range of ethnicities. Baseline delirium was excluded. Delirium was assessed using the MDAS, the RASS and the Nursing Delirium Screening Scale (Nu-DESC). The study found no evidence to support the effectiveness of the hydration intervention on delirium symptoms [at 7 days from baseline, mean difference in MDAS score = -0.50 (95% CI: -4.57−3.57); $P = 0.81$]. There was also no evidence of effect on pain, QoL or survival. The strength of findings was downgraded to low because of incomplete outcomes data and the relatively small number of study participants.

No completed RCTs of non-pharmacological interventions for the treatment of delirium were found. The ongoing feasibility trial identified did not distinguish between prevention and treatment [113]. Therefore, the scope of the search was expanded to include reports of non-randomised trials of single or multicomponent non-pharmacological interventions for the management of delirium, which identified one additional study [114] (see Supplementary Table S5, available at *Annals of Oncology* online). In a non-randomised prospective comparative cohort study in 1516 terminally ill cancer patients (without delirium at baseline), Gagnon et al. [114] evaluated the effectiveness of a multicomponent intervention [comprising structured assessment of risk factors for delirium (including medications), daily orientation of the patient and education of a family member]. Inpatients at two Canadian palliative care centres received the intervention ($N = 674$), with five centres providing 'usual care' ($N = 842$). Compared with usual care, the intervention was not effective in preventing delirium, reducing delirium severity or reducing the number of days with delirium. However, there were a number of substantive methodological limitations, in addition to the lack of randomisation. These include the strong possibility of contamination and delirium misclassification bias, and the variable implementation of the intervention (see also the section 'Pharmacological interventions for delirium prevention and treatment in adults with cancer').

The striking finding overall is the paucity of high-quality research on non-pharmacological strategies for delirium prevention and treatment in adult patients with cancer. This is despite the considerable burden of disease attributable to delirium in this population.

Recommendations:
- For most non-pharmacological interventions for the prevention or treatment of delirium in cancer patients, there is no

research evidence on which to base recommendations for practice [V, C].
- Clinically assisted hydration is not more effective than placebo in preventing delirium [II, C].
  ○ There is low-quality evidence from one RCT.

Pharmacological interventions for delirium prevention and treatment in adults with cancer

Pharmacological underpinnings

Although it is now recognised that there are potentially many neurotransmitter derangements associated with delirium [115], the cerebral imbalance resulting in a relative excess of dopaminergic and deficiency of cholinergic transmission has been one of the main proposed mechanisms in the neuropathogenesis of delirium; it has also provided a target mechanism or basis for much of the strategic approach in the pharmacological prevention and treatment of delirium over the past two decades with antipsychotics (dopamine D_2 receptor antagonists) used historically in delirium management. Other postulated pathophysiological mechanisms of delirium include: cortisol abnormalities, stress reaction, inflammation and cerebral oxidative metabolism disturbances [1, 115].

Pharmacological interventions for delirium prevention in adults with cancer

The initial literature search identified no studies that met the authors' inclusion criteria (see Supplementary Figure S2, available at *Annals of Oncology* online). Of interest, only one study in cancer patients examined, at least in part, a pharmacological preventive strategy [114]. In addition to non-pharmacological interventions (described previously in the section 'Non-pharmacological interventions for delirium prevention and treatment in adults with cancer'), this non-randomised prospective cohort study included a pharmacological risk alert intervention for physicians. The standardised delirium risk alert intervention focused on three medication categories: (i) opioids, dose > 80 mg of parenteral morphine equivalent per day; (ii) benzodiazepines, dose ≥ 2 mg lorazepam equivalent per day; and (iii) anticholinergics, corticosteroids and anticonvulsants intake. The patient's attending physician was made aware of these pharmacological risk factors when present. Although the adherence for completion of the risk alert process was 91.2%, the entire multicomponent preventive strategy did not differ from routine care in relation to the incidence, severity or duration of the patient's first inpatient episode of delirium. In addition to the previously stated study limitations, the degree to which attending physicians specifically adjusted medications or deprescribed on the basis of the risk alert intervention was not reported.

Deprescribing. Deprescribing refers to the systematic process of dose reduction or stopping medications that are potentially harmful or deemed to be no longer beneficial [116]. The strategy of deprescribing has been studied mostly in older patients and

less so in patients specifically with cancer, though most cancer patients are in older age groups and polypharmacy is a frequent problem for them [117]. While many literature reports focus on individual drugs for delirium risk, there is also a need to consider the cumulative risk in association with polypharmacy. Polypharmacy is associated with increased anticholinergic burden in advanced cancer and likely reflects the increasing use of medications with anticholinergic activity for symptom control in association with advanced disease [118]. Various methods, including rating scales and serum assays, have been developed as measures of anticholinergic activity, but the lack of standardised measures among these methods has hindered study comparison [119]. Studies have examined the association of anticholinergic drug burden exposure with the risk of cognitive decline [120] and, to a lesser extent, delirium, with somewhat conflicting findings; the association with delirium was negative in a critical care study [121] and an elderly care study [122], but was positive in two studies in palliative care [123, 124]. A population database study demonstrated a significant association between anticholinergic drug burden and the development of an anticholinergic event, including delirium [125]. The Drug Burden Index (DBI) is a validated tool that non-invasively measures exposure not only to anticholinergic but also sedative drug load [126]. A retrospective study in a geriatric medicine setting found that patients with a high DBI were almost three times more likely to be admitted for delirium than those with no DBI exposure [127]. Collectively, despite standardisation shortcomings in relation to the measure of drug anticholinergic burden, studies of polypharmacy (mostly in older patients and to a lesser extent in palliative care) do provide some evidence of a delirium risk in association with anticholinergic and sedative drug burden.

Recommendations:
- Given the absence of studies evaluating pharmacological prevention of delirium in cancer patients, no evidence-based recommendations are proposed [V, C].
  - Readers are referred to other published guidelines that examine the evidence for pharmacological prevention of delirium in adult patients [69].
- Based on available evidence, deprescribing would appear to be worthwhile in older patients for many reasons, although there is insufficient data to support this recommendation for all cancer patients from the specific perspective of delirium prevention [V, B].
  - Other benefits of deprescribing in cancer patients include the identification of drug–drug interactions and minimisation of polypharmacy [117, 128].
  - Prescribers should also ensure that the inappropriate prescribing of medication is avoided.

Pharmacological interventions for delirium treatment in adults with cancer

The literature search and subsequent review yielded 14 studies to inform potential guideline recommendations in relation to pharmacological management of delirium (see supplementary Figure S2 and Table S6, available at *Annals of Oncology* online). After our search was completed, a relevant RCT was published [129] and was deemed important to add to our search findings,

yielding a total of 15 studies. Of the included studies, three were RCTs [129–131], seven were prospective cohort studies [80, 81, 132–136] and the remaining five were retrospective cohort studies [83, 137–140]. These studies were published between 2000 and 2017, and the study sample sizes ranged from $N = 14$ to $N = 247$; this resulted in the cumulative evaluated $N = 881$. The pharmacological interventions evaluated were antipsychotics (risperidone, $N = 4$; haloperidol, $N = 3$; olanzapine, $N = 3$; quetiapine, $N = 1$; aripiprazole, $N = 3$); a psychostimulant (methylphenidate, $N = 1$); a benzodiazepine (midazolam, $N = 1$; lorazepam, $N = 1$); and opioid rotation or switching (fentanyl to methadone, $N = 1$; morphine to fentanyl, $N = 1$; various opioids to methadone, $N = 1$). A total of 843/881 patients (96%) enrolled in these studies had a cancer diagnosis. Of note, it appears that the aripiprazole groups in the three retrospective studies by Boettger et al. [137, 138, 140] are the same across all three studies ($N = 21$) but for the purpose of this review, these studies are described separately.

Of the three RCTs, the smallest one (Kim et al.; $N = 32$; 72% with a cancer diagnosis) compared risperidone with olanzapine over a 7-day period; dose titration was allowed, and a rater-blind study design was used [130]. The blinded severity ratings were conducted using a validated tool. All patients showed a statistically significant improvement from baseline and there was no significant difference in either efficacy or adverse effects between risperidone and olanzapine. Approximately one in three and one in five patients in each treatment group experienced daytime somnolence and extrapyramidal side effects (EPSEs), respectively. The second study (Hui et al.) was a single-centre, double-blind, parallel group RCT conducted in adult patients with advanced cancer who were admitted to an APCU at a tertiary cancer centre in the US and had developed delirium [diagnosed according to DSM Fourth Edition, Text Revision (DSM-IV-TR) criteria] and had a RASS score of $\geq +2$ (i.e. 'agitated') in the previous 24 hours despite scheduled haloperidol [129]. Once enrolled, patients started a standardised open-label regimen of haloperidol 2 mg i.v. every 4 hours and 2 mg every 1 hour as needed for 'agitation', at the discretion of the clinical team (attending physician and bedside nurse). If a patient's monitored RASS score was $\geq +2$ (this threshold was changed to a RASS score of $\geq +1$ after the study had been recruiting for 7 months), they were then randomised to receive i.v. 3 mg lorazepam followed by 2 mg haloperidol ($N = 29$), or a placebo and 2 mg haloperidol ($N = 29$). After haloperidol dose standardisation, only 58/90 randomised patients developed further agitation requiring the blinded intervention. The primary study outcome was the RASS score assessed 8 hours after the intervention medications, with a greater reduction in the lorazepam/haloperidol arm of -4.1 points from baseline RASS score compared with -2.3 points in placebo/haloperidol arm. The mean difference in the RASS score between the two groups (95% CI) was -1.9 points (-2.8 to -0.9, $P < 0.001$). The third study (Agar et al.) was a large three-armed, placebo controlled multicentre trial ($N = 247$; 88% with a cancer diagnosis) conducted in 11 inpatient hospice or hospital palliative care services that compared age-adjusted and titratable doses of risperidone and haloperidol with a placebo control [131]. There were no statistically significant differences among the three groups at baseline, including symptom severity scores on either the MDAS or the Nu-DESC. The study was conducted over a

72-hour period with relative change in specific target symptom severity scores (inappropriate communication or behaviour or perceptual disturbance, as rated by nurses) as primary outcome. Compared with placebo, treatment with either risperidone or haloperidol was associated with higher delirium symptom severity scores and more EPSEs. As a secondary outcome, haloperidol treatment was associated with poorer overall survival in long-term follow-up.

Of the seven prospective cohort studies ($N = 210$ patients in total), six had no active comparator medication; study comparisons were made on a longitudinal, before-versus-after basis in terms of delirium symptom severity measures [80, 81, 132–135]. Improvement compared with baseline was demonstrated in two studies for olanzapine: response rates were 76% at day 7 [132] and 38% at day 3 [134] for oral and s.c. administered olanzapine, respectively. Improvement was also demonstrated for oral risperidone with a 48% response rate (a 25% reduction in delirium severity scores) at day 7 and mild sedation occurred in one patient [135]. In a study of morphine-associated delirium, an opioid switch to fentanyl resulted in a day 7 response (MDAS score < 10) rate of 90% [81]. Similarly, in transdermal fentanyl-associated delirium, 4/5 (80%) patients had a resolution of delirium by 7 days following an opioid switch to methadone [80]. Daily methylphenidate administration for hypoactive delirium with no delusional or perceptual disturbance and no identifiable underlying cause for delirium was associated with cognitive improvement in all 14 patients [133]. The remaining prospective cohort study compared aggregate delirium severity responses with short (quetiapine) versus long (haloperidol, risperidone and olanzapine) half-life antipsychotics and broader multi-acting receptor-targeted antipsychotics (MARTAs: olanzapine and quetiapine) versus narrower non-MARTAs (haloperidol and risperidone) [136]. Compared with baseline, there was improvement in MDAS scores at day 3 in all medication groups, but only the short-acting and MARTAs groups continued to show a statistically significant improvement at day 7 of treatment.

Of the five retrospective cohort studies ($N = 302$ patients in total), three had no active comparator medication and study comparisons were made on a longitudinal, before-versus-after basis in terms of delirium symptom severity measures [82, 137, 139]; the remaining two studies used case-matched controls who were receiving haloperidol [138, 140]. In the management of opioid-associated delirium, a switch to methadone resulted in improved delirium symptom scores after 48 hours, as reflected by > 50% reduction in their mean baseline MDAS score [82]. In three separately reported studies from the same centre, patients treated with aripiprazole over 7 days showed improvement of delirium symptoms, as reflected by > 50% reduction in mean MDAS scores compared with baseline [137, 138, 140]. When compared with similar patients treated with haloperidol, risperidone and olanzapine, aripiprazole treatment was associated with no difference in efficacy but fewer adverse events [138, 140]. A study using an algorithmic protocol for routine practice that specified initial 5 mg doses of both haloperidol and midazolam administered intramuscularly, and subsequent adjusted s.c. doses administered at 30-minute intervals depending on response, reported an improvement in delirium symptoms when compared with baseline in 91% of 584 episodes occurring in 135 (9%) of their patient PCU admissions for whom the protocol was deemed necessary [139]. The reported improvement was subjective on the part of healthcare providers, as there was no report of a standardised tool used to assess delirium severity. Transient sedation was reported without a frequency estimate.

Methodological issues such as small sample size, selection and misclassification bias were identified with many of the studies included in our review. However, the major methodological concern is the absence of a comparator placebo arm in many studies examining pharmacological interventions for delirium symptom management. The reversibility of delirium in a PCU has been reported to be as high as 50% following the standard recommended approach of treating reversible precipitating factors [12]. In the absence of a placebo arm, the improvements in delirium noted in a cohort study may be explained by a response to treatment of the delirium episode's precipitants rather than a response to an antipsychotic. One of the included RCTs was the first study to examine pharmacological management of delirium symptoms in (mainly) cancer patients, albeit that most had advanced disease [131]. This study clearly demonstrated no benefit with risperidone or haloperidol in the relief of distressing target symptoms of delirium; in fact, these symptoms were worse with both of the antipsychotics than with placebo. Remarkably, no patients in this study had severe delirium, which limits the generalisability of study findings in relation to the severe episodes of delirium that can occur in cancer patients, especially in the context of advanced disease. Nonetheless, the findings of this study are consistent with similar studies that failed to demonstrate a beneficial role for haloperidol or antipsychotics in general in the pharmacological management of delirium in critical care [141, 142]. Three recent systematic reviews (one relating solely to haloperidol) and two meta-analyses of the pharmacological management of delirium in hospitalised patients have also concluded that there is insufficient or no clear evidence to support haloperidol or antipsychotics in general in either the prevention or treatment of delirium [111, 143, 144].

Recommendations:

- Opioid rotation (or switching) to fentanyl or methadone is an efficacious strategy in the context of opioid-associated delirium [V, B].
  - The standard approach to opioid-associated delirium in clinical practice is to reduce the dose or switch to a different opioid (with a reduction in opioid equianalgesic dose by ∼30%–50%) [145].
- Administration of either haloperidol or risperidone has no demonstrable benefit in the symptomatic management of mild-to-moderate delirium and is not recommended in this context [I, D].
  - In clinical practice, it may be difficult to clearly categorise delirium as mild or moderate, especially since delirium by its very nature tends to fluctuate in its presenting symptoms. As haloperidol and risperidone are not beneficial in cancer patients with mild-to-moderate delirium [131], and have been shown to worsen symptoms, by logical extension it can be argued that these medications will also likely not be of benefit and may be harmful in delirium categorised as severe. Further trials of antipsychotics in severe delirium, including subgroup analyses in relation to different precipitating factors, phenomenology and symptom expression, are required to confirm this, but based on emerging data and systematic

reviews, it is suggested that these concerns relate to both older and newer generation antipsychotics as a class.

- Administration of olanzapine may offer benefit in the symptomatic management of delirium [III, C].
- Administration of quetiapine may offer benefit in the symptomatic management of delirium [V, C].
- Administration of aripiprazole may offer benefit in the symptomatic management of delirium [IV, C].
  - ○ Olanzapine, quetiapine and aripiprazole appear less likely to be associated with EPSEs than first generation antipsychotics. Quetiapine is available in oral formulations only for acute management, while olanzapine and aripiprazole are also available in parenteral or orally dispersible formulations in some countries. Sedation is a well-recognised side effect of olanzapine and quetiapine, which may be advantageous in patients with hyperactive delirium.
- Methylphenidate may improve cognition in hypoactive delirium in which neither delusions nor perceptual disturbance are present and for which no cause has been identified [V, C].
- Benzodiazepines are effective at providing sedation and potentially anxiolysis in the acute management of severe symptomatic distress associated with delirium [II, C].
  - ○ Although midazolam and other benzodiazepines are used very extensively in palliative care for multiple reasons, they are not considered part of the initial strategy in delirium management. This is because benzodiazepines are sedating, have been identified as deliriogenic and, in those with some functional mobility, are associated with a clear risk of falls. The clinical decision to use midazolam or lorazepam as a crisis intervention in delirium management (particularly in patients who are agitated and regardless of whether they are already on an antipsychotic), must involve an assessment of the level of patient distress; the safety risks with and without administering benzodiazepines; and patient mobility. However, benzodiazepines do have a role as first-line agents in the management of alcohol or benzodiazepine withdrawal.

Practice point: the use of pharmacological interventions in the management of delirium in adults should be limited to patients who have distressing delirium symptoms (such as perceptual disturbances) or if there are safety concerns where the patient is a potential risk to themselves or others. In order to achieve the appropriate balance between benefit and potential harm, medications should be used in the lowest effective dose and for a short period of time only (see Table 4 and Figure 1).

Experiential impact of delirium, support and education

Experiential impact of delirium

A delirious patient may experience strong emotions, feel anxious and threatened and present as verbally and physically aggressive or withdrawn [1, 146]. Vivid hallucinations or illusions may provoke overwhelming fear. Patients often feel a lack of control, in addition to sensing that they are not being listened to or understood [1].

Delirium causes significant distress. In both quantitative and qualitative studies, cancer patients who have recovered from an episode of delirium confirm that the experience is distressing,

even for those with hypoactive delirium [147–149]. Family members may feel helpless and distressed, especially if observing agitated behaviours and hallucinations or if having difficulty communicating with the patient at the time of the delirium episode [147–152], with their distress continuing into bereavement [146]. Caring for an agitated delirious patient is also distressing for oncology and palliative care nursing staff [7, 147, 153]. In addition to being provided information about delirium, patients may require a more formal opportunity to debrief after the delirium episode has resolved [1]. Nurses and other members of the healthcare team should be offered a formal team debriefing session after challenging cases [7].

Informational and support needs for the family

Symptoms of delirium (see Table 2), including cognitive, perceptual and emotional disturbances, can dominate the clinical picture, causing high levels of emotional distress for families observing often sudden and profound behavioural and psychological disturbances in their loved ones. As a patient approaches the final days and hours of life, the consequent difficulty that families have in maintaining communication and relationships with those experiencing delirium may compound self-reported feelings of helplessness, inadequacy, despair and anger at the sense of 'loss' of the person before their physical death [152, 154].

Significant improvements in delirium and the management of symptoms are possible—even at the end of life, helping to reduce distress for the patient, their family and staff [155]. Usually close to the bedside for extended periods of time, families are also uniquely placed to observe and report changes that may indicate the occurrence of delirium, offering clinicians the opportunity for prompt intervention. Families may also assist in delivering non-pharmacological interventions [156].

Most families will have limited prior knowledge or experience of delirium in advanced cancer. This lack of understanding can worsen their distress, especially, for example, when they incorrectly assume that a particular delirium episode has been caused by medication or unmanaged pain [149, 155]. Information about delirium given in the form of a leaflet/brochure designed for relatives can improve understanding and preparedness, thus ameliorating at least some distress and increasing the competence and confidence of families to respond in this situation [155, 157]. If delirium develops, studies further suggest that supplementing the provision of written information with educational and psychological support for families from suitably prepared nursing and other healthcare staff is maximally effective [149, 154, 158].

Recommendations:

- While not all patients with cancer will develop delirium, we recommend that relatives have access to information about delirium pre-emptively and at repeated intervals, especially if the patient's condition is declining due to disease progression. This information should also be disseminated to the wider family who are likely to visit [V, A].
- If delirium develops, written information should be supplemented with educational and psychological support for families by suitably trained staff [V, A].

Table 4. Pharmacological interventions that may have a role in the management of delirium symptoms in adult patients (derived from [101, 171, 176–178])		
Medication	**Suggested starting dose**	**Comments**
First-generation antipsychotics		
Haloperidol	0.5–1 mg p.o. or s.c. stat. PRN dose: 0.5 or 1 mg p.o. or s.c. q1h PRN (give q8h–q12h if scheduled dosing required) Use lower doses in older or frail patients, e.g. 0.25–0.5 mg, and titrate gradually Can also be given i.v. (need ECG monitoring) and i.m.	May cause EPSEs Do not use if patient has Parkinson's disease or dementia with Lewy bodies due to risk of EPSEs May prolong QTc interval
Methotrimeprazine (Levomepromazine)	5–12.5 mg p.o. or s.c. stat. PRN dose: 5–12.5 mg p.o./s.c. q2h PRN (Give q8h–q12h if scheduled dosing required) Use lower doses in older or frail patients, e.g. 2.5 mg, and titrate gradually Can also be given by deep i.m. injection	Sedating, anticholinergic effects May cause EPSEs, orthostatic hypotension, paradoxical agitation s.c. injection may cause irriation (In some countries, tablet available in 6-mg dose, rather than 5 mg)
Chlorpromazine	12.5–25 mg p.o. or p.r. stat. (Give q6h–q12h if scheduled dosing required) In older patients, use doses in the lower range Use with caution in patients with renal and hepatic impairment Can also be given slow i.v. (diluted) or i.v. infusion, deep i.m. injection	Sedating, anticholinergic effects May cause EPSEs, orthostatic hypotension May prolong QTc interval Parenteral use may cause local irritation
Second-generation antipsychotics		
Olanzapine	2.5–5 mg p.o. or s.c. stat. (If scheduled dosing required, start with 2.5–5 mg p.o. or s.c. daily—usually at bedtime) Reduce dose in older patients and patients with hepatic impairment Available as ODT Can also be given i.m.	May cause drowsiness, orthostatic hypotension Metabolic effects (long-term use) (Caution: combining with benzodiazepine as risk of oversedation and respiratory depression)
Quetiapine	25 mg (immediate release) p.o. stat. (Give q12h if scheduled dosing required) Reduce dose in older patients and patients with hepatic impairment Oral route only	Sedating Less likely to cause EPSEs than another atypical AP May cause orthostatic hypotension, dizziness
Risperidone	0.5 mg p.o. stat. (Give up to q12h if scheduled dosing required) Reduce dose in older patients and patients with severe renal or hepatic impairment Available as ODT Oral route only	Increased risk of EPSEs if dose > 6 mg/24 h May cause insomnia, agitation, anxiety, drowsiness, orthostatic hypotension
Third-generation antipsychotics		
Aripiprazole	5 mg p.o. or i.m. (immediate-release) stat (Give q24h if scheduled dosing required) Reduce dose in older patients and in poor metabolisers of cytochrome P450 2D6 Available as ODT and oral solution	Less likely to cause EPSEs May cause headache, agitation, anxiety, insomnia, dizziness, drowsiness (Caution: cytochrome P450 2D6 and 3A4 drug–drug interactions; consult pharmacist/pharmacy references for further details)
Benzodiazepines		
Treatment of choice as monotherapy for alcohol or benzodiazepine withdrawal	[Caution: in patients with severe pulmonary insufficiency, severe liver disease, myasthenia gravis (unless using in imminently dying patient)]	(Caution: fatalities have been reported with concurrent use of benzodiazepines with high-dose olanzapine)

Continued

Table 4. *Continued*		
Medication	**Suggested starting dose**	**Comments**
Midazolam	2.5 mg s.c. or i.v. q1h PRN (up to 5 mg maximum) Use lower doses in older or frail patients or in patients with COPD, or if co-administered with an AP, e.g. 0.5–1 mg s.c./i.v. q1h PRN Can also be given i.m.	Increased risk of falls May cause delirium, drowsiness, dizziness, paradoxical agitation, anxiety, insomnia May have a role as a crisis medication in the management of delirious patients with severe agitation and distress
Lorazepam	1 mg s.c. or i.v. stat. (up to 2 mg maximum) Use lower doses in older or frail patients or in patients with COPD, or if co-administered with an AP, e.g. 0.25–0.5 mg s.c./i.v. q1h PRN Can also be given p.o., s.l.	Increased risk of falls May cause delirium, drowsiness, paradoxical agitation s.c. injection may cause irritation May have a role as a crisis medication in the management of delirious patients with severe agitation and distress

At this time, there is limited research evidence for the use and dosing of these medications for the management of delirium in patients with cancer. Antipsychotics and benzodiazepines can themselves cause increased patient agitation and delirium.

Short-term use of medications in the lowest effective dose (e.g. antipsychotics or benzodiazepines) may have a role in delirium management if the patient has perceptual disturbances (e.g. hallucinations, illusions), or if the patient is severely agitated and is a potential risk to themselves or others. Medications for delirium symptom management should be initially started on a PRN (as needed) basis. Regular (or scheduled) dosing may be required for persistent distressing delirium symptoms and should be given for the shortest period of time possible.

The reader should note that no medication is currently licenced for use (worldwide) in the management of delirium. Availability of formulations and doses may vary according to individual countries. While every effort has been made to ensure the accuracy of this text and medication doses, please also consult a pharmacist and/or pharmacy references and the manufacturer's Summary of Product Characteristics when prescribing these medications.

AP, antipsychotic; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EPSE, extrapyramidal side effect; i.m., intramuscular; i.v., intravenous; ODT, oral disintegrating tablet; p.o., oral; p.r., per rectum; PRN, when required; QTc interval, rate-corrected QT interval; qXh, every X hours; s.c., subcutaneous; s.l., sublingual; stat., immediately.

Recommended content of leaflet/brochure on delirium:
- A definition of delirium, specifying causes, symptoms, evolution and management.
- An explanation of the fluctuating nature of delirium, e.g. periods of confusion may alternate with periods of lucidity.
- Guidance on appropriate responses and non-pharmacological interventions that may be helpful.

Educational needs of nurses and other members of the healthcare team

In a cross-sectional questionnaire study of 88 Japanese oncology nurses following a 1.5-hour training session of cancer patients' mental health needs, 57% reported feeling very or extremely concerned about assessing for delirium and 66% felt very or extremely concerned about caring for delirious patients [159]. As a component of a large cross-sectional questionnaire survey (79% response rate) of 3008 nurses caring for oncology patients in Japan, the Palliative Care Self-Reported Practices Scale scored low for delirium care [160]. Nurses may be uncertain regarding how to assess and best manage a patient's delirium, and may feel isolated on evening and night shifts [7]. As a result, nurses have reported a need to improve their delirium knowledge and assessment [7, 153].

In an RCT of 96 Japanese oncology nurses (with a waiting list control group) [161], 50 participants in the intervention group received a 16-hour psycho-oncology training program, which included delirium and suicidal ideation in addition to the topics of patients' normal and distress reactions to cancer. Knowledge, self-reported confidence and attitude scales were completed pre-intervention and 3 months post-intervention as a mailed survey.

There was significant improvement in both the knowledge and confidence scores in the intervention group, but not in attitudes. No effect was found on the secondary outcomes: work-related distress and burnout.

In a repeated-measures evaluation of a 2-hour delirium education session delivered to 23 registered nurses, followed by the implementation of a delirium protocol on a 24-bed inpatient oncology unit in the US, delirium knowledge increased from 69% pre-test to 86% post-test, and 81% at 11 months [162]. Nurses' confidence in managing delirious patients increased from 47% to 66%, rising to 69% at 11 months.

A systematic review of interprofessional delirium education studies concluded that combining interprofessional education interventions with interprofessional clinical practice activities or procedures may improve patient outcomes and healthcare team performance [163].

Recommendation:
- Interprofessional delirium education interventions should be a core component of an interprofessional unit- or hospital-wide strategy to improve the recognition, assessment and management of delirium by the whole healthcare team [II, A].

Management of refractory delirium in the actively dying patient

In the dying phase, delirium is usually refractory. For ongoing distressing delirium-related agitation in the final hours, days or

Table 5. Summary of recommendations

Clinical assessment, diagnosis and screening
- The diagnosis of delirium should be made by a trained and competent healthcare professional using a clinical assessment based on DSM or ICD criteria [III, C]
- The evidence is insufficient to recommend the routine use of screening tools in making a diagnosis of delirium in cancer patients [III, C]
- If any changes in cognitive or emotional behaviour or psychomotor activity suggestive of delirium are present, a trained healthcare professional with expertise in evaluating delirium should carry out a clinical assessment to confirm the diagnosis of delirium [III, C]
- The evidence is insufficient to recommend for or against the routine use of tools to assess delirium severity in daily practice [III, C]

Management of potentially reversible causes of the delirium episode
- For cancer patients whose assessments indicate delirium, identify the predisposing and precipitating factors through a comprehensive initial assessment [III, A]
- Opioid rotation (or switching) may be appropriate if signs of OIN are present [V, B]
- There is limited research evidence for the role of clinically assisted hydration in the symptomatic management of delirium [V, C]
- Infection considered to be a precipitating factor for delirium should be treated, if in accordance with a patient's goals of care and illness trajectory [V, C]
- Bisphosphonates (such as i.v. pamidronate and zoledronic acid) may control hypercalcaemia and reverse delirium in a substantial number of cases [I, A]
- The discontinuation of implicated medications, fluid restriction and adequate oral salt intake is recommended for the management of confirmed SIADH [V, C]
- Magnesium replacement is recommended for the management of hypomagnesaemia [V, C]
- Medication or therapy withdrawal is recommended in patients with delirium related to anticancer treatments such as chemotherapy and immunotherapies [V, C]

Non-pharmacological interventions for delirium prevention and treatment in adults with cancer
- For most non-pharmacological interventions for the prevention or treatment of delirium in cancer patients, there is no research evidence on which to base recommendations for practice [V, C]
- Clinically assisted hydration is not more effective than placebo in preventing delirium [II, C]

Pharmacological interventions for delirium prevention and treatment in adults with cancer
- Given the absence of studies evaluating pharmacological prevention of delirium in cancer patients, no evidence-based recommendations are proposed [V, C]
- Based on available evidence, deprescribing would appear to be worthwhile in older patients for many reasons, although there is insufficient data to support this recommendation for all cancer patients from the specific perspective of delirium prevention [V, B]
- Opioid rotation (or switching) to fentanyl or methadone is an efficacious strategy in the context of opioid-associated delirium [V, B]
- Administration of either haloperidol or risperidone has no demonstrable benefit in the symptomatic management of mild-to-moderate delirium and is not recommended in this context [I, D]
- Administration of olanzapine may offer benefit in the symptomatic management of delirium [III, C]
- Administration of quetiapine may offer benefit in the symptomatic management of delirium [V, C]
- Administration of aripiprazole may offer benefit in the symptomatic management of delirium [IV, C]
- Methylphenidate may improve cognition in hypoactive delirium in which neither delusions nor perceptual disturbance are present and for which no cause has been identified [V, C]
- Benzodiazepines are effective at providing sedation and potentially anxiolysis in the acute management of severe symptomatic distress associated with delirium [II, C]

Experiential impact of delirium, support and education
- While not all patients with cancer will develop delirium, we recommend that relatives have access to information about delirium pre-emptively and at repeated intervals, especially if the patient's condition is declining due to disease progression. This information should also be disseminated to the wider family who are likely to visit [V, A]
- If delirium develops, written information should be supplemented with educational and psychological support for families by suitably trained staff [V, A]
- Interprofessional delirium education interventions should be a core component of an interprofessional unit- or hospital-wide strategy to improve the recognition, assessment and management of delirium by the whole healthcare team [II, A]

DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; i.v., intravenous; OIN, opioid-induced neurotoxicity; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

1–2 weeks of life, pharmacological sedative management in the form of palliative sedation may be required [76]. A systematic review by Maltoni et al. reported that refractory delirium is the most frequent indication for palliative sedation [164]. Further research is needed on the efficacy of palliative sedation on symptom control and QoL [165]. After careful assessment by the interprofessional team and/or specialist palliative care team before commencement, the level of prescribed medication for palliative sedation should be proportionate to the severity of the intractable symptom(s), and frequently monitored using a tool such as the RASS [166] or the palliative version, the RASS-PAL [167]. Families require increased support and information from

Table 6. Summary of recommendations for future research

- To examine methods of improving delirium detection in cancer patients by all members of the healthcare team (including physicians, nurses, allied health and family caregivers) across clinical care settings
- To examine the validity of delirium diagnostic tools in the cancer population and the clinical effectiveness and harms and the cost-effectiveness of such tools
- To conduct validation studies of delirium screening tools in the cancer population across clinical care settings
- To conduct RCTs exploring the clinical effectiveness and harms and the cost-effectiveness of delirium screening in the cancer population across different care settings
- To evaluate the role of delirium severity assessment in daily clinical practice
- To examine the association between delirium duration and outcomes in the cancer population
- To develop and validate delirium risk prediction models for incident delirium in oncology patients
- To develop and validate delirium prediction models for treatment response/reversibility of delirium in patients with advanced cancer
- To conduct randomised trials to evaluate the practices of opioid rotation (switching to opioids other than fentanyl and methadone) and of clinically assisted hydration in delirious patients
- To undertake studies of 'deprescribing' in the cancer population to evaluate its potential role in the prevention of delirium
- To conduct robust and adequately powered RCTs of non-pharmacological multicomponent interventions targeting specific risk factors for delirium in cancer patients in addition to environmental and social contributing factors. These RCTs should be designed to assess comparative effectiveness and harms, achieve the target sample size and incorporate blinding of outcome assessors
- To undertake mixed methods studies to inform the optimal approach to implementation of often complex non-pharmacological multicomponent interventions
- Undertake economic evaluations to determine the cost-effectiveness of non-pharmacological multicomponent interventions in resource-constrained healthcare settings
- To conduct prospective RCTs examining both the pharmacological prevention and treatment of delirium in patients with a cancer diagnosis. These studies should incorporate a placebo group to establish effectiveness and safety before comparative efficacy studies are conducted
- To conduct studies that evaluate the role of levomepromazine (methotrimeprazine), an antipsychotic that is commonly used by the subcutaneous route in palliative care for the management of agitated delirium at the end of life. Further research is required to examine the efficacy and harms of levomepromazine, as the authors' literature search did not find any published studies that addressed this issue
- To conduct studies of novel pharmacotherapeutic agents such as melatonin, which may have a role in preventing and treating delirium in cancer patients given the evidence supporting such use in other populations and settings
- To conduct studies examining the optimal pharmacological management of severe refractory delirium in patients dying with advanced cancer
- To perform laboratory studies to better elucidate the complex neuropathogenesis of delirium and thus better guide the ultimate pharmacological targeting of pivotal neurotransmitter pathways and their receptors

RCT, randomised controlled trial.

the healthcare team during this time. (See also the ESMO CPG for the management of refractory symptoms at the end of life and the use of palliative sedation [168]).

Suggestions for further research

A summary of recommendations is shown in Table 5. In addition, the Guideline Development Group (GDG) made several recommendations for future research (see Table 6). As age is a significant risk factor for delirium, important considerations for future research are the association of cancer with older age groups and the projected demographic changes with an increasing elderly proportion of the population. Thus, in designing delirium research studies, the challenges of recruitment and the high rate of attrition in this often-frail population are important issues to address to avoid inadequately powered trials.

As there are usually multiple factors contributing to a delirium episode in any cancer patient, further research is needed to establish the effectiveness of multiple interventions across healthcare settings: hospitals, palliative care or hospice inpatient units and community. Many studies for multicomponent, non-pharmacological interventions in older adults have been conducted in other settings. Studies

with a focus on the multidisciplinary non-pharmacological prevention and treatment of delirium in adults with cancer, particularly adults $\geq$ 65 years old and in non-perioperative settings, are urgently needed.

Conclusion

Delirium is a clinical emergency and an index of acute change in a patient's medical condition. The effective recognition, assessment and management of an episode of delirium hinges on vigilance and commitment by the whole healthcare team. Although reversal of delirium may not always be possible or desirable, symptomatic management, primarily with non-pharmacological strategies should be made available to all patients and supplemented with pharmacological intervention if necessary. Psychological support should also be made available to all patients and their families.

For many of the domains reviewed by the GDG, the level of evidence was low; hence, the linked grade of recommendation was not strong. In addition, no evidence was found for most non-pharmacological interventions for the prevention or treatment of delirium in cancer patients. There is an urgent need for adequately

Table 7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [179].

powered and robust clinical trials of non-pharmacological and pharmacological interventions, including RCTs, to improve the prevention and management of this distressing syndrome.

Methodology

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

A review of the evidence underpinning each section topic for this CPG was assigned to 1–3 members of the multidisciplinary, core GDG. The literature search varied according to each guideline section, and included the Cochrane, Ovid Medline, PubMed, Embase, PsycINFO and SCOPUS databases for the years 2000 until May 2017. Relevant studies in cancer patients that were subsequently published from June to 19 September 2017 were reviewed on an individual basis by the relevant section authors before inclusion. Databases were searched using relevant subject headings and free-text terms. Study inclusion criteria were: adults ≥ 18 years old with cancer and either at risk of delirium or with a formal delirium diagnosis; and hospital, inpatient palliative care/hospice and community settings. Paediatric populations and alcohol withdrawal delirium (delirium tremens) were excluded. For the literature searches for pharmacological prevention and treatment and screening and diagnostic tools, studies in which the study population was comprised of $< 50\%$ cancer patients were excluded. Perioperative delirium and intensive or critical care settings were excluded, as current evidence-based guidelines are available for these populations [169, 170]. Case reports, case series, conference abstracts, reviews, editorials and letters were also excluded.

SB coordinated the GDG, led the experiential impact and management of refractory delirium sections, contributed to the non-pharmacological, pharmacological, educational needs, management of potentially reversible causes and epidemiology sections, edited the remaining sections and drafted the manuscript. PL contributed to pharmacological section and helped to draft the manuscript. KR contributed to delirium diagnosis and screening section and helped to draft the manuscript. CC led the section on management of potentially reversible causes. MLu led the section on risk factors. SK contributed to pharmacological section. NSi led the non-pharmacological section. AM contributed to delirium diagnosis and screening section. DD led the section on delirium outcomes. MLa led the section on epidemiology. NSc led the section on informational and support needs. EB contributed to the educational needs section. CR is ESMO Subject Editor and assisted with coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Disclosure

The authors have declared no conflicts of interest.

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