Clinical characteristics and treatment of delirium in palliative care settings

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Summary Delirium is commonly seen in palliative care. It usually develops over a short period of time and is characterized by a disturbance of attention and awareness. As delirium is associated with increased mortality, prevention and early identification of this severe neurocognitive disorder is of high clinical relevance. This paper provides a brief overview of risk factors, preventive measures, current screening and diagnostic procedures, as well as nonpharmacological and pharmacological treatment options of delirium in the palliative care setting.

Keywords Confusion · Diagnosis · Symptom assessment · Prevention and control · Drug therapy

Delirium is frequent(ly missed) in the palliative care setting

Delirium is a neurocognitive disorder commonly seen in palliative care and the critically ill. According to an updated systematic review up to three quarters of palliative inpatients are affected, with a pooled point prevalence on admission of 35% and a prevalence of up to 88% prior to death [1]. The illness is generally associated with an increased short-term as well as long-term mortality and prolonged stay in intensive care [2, 3]. Furthermore, delirium is a predictor of adverse outcome [4]. Apart from the exorbitant financial burden there is also evidence that delirium causes enormous distress for caregivers [5, 6]. Despite its severity and frequency, delirium is still underdiagnosed and often missed [7]. Timely diagnosis

of this acute condition is essential as it is potentially reversible, e.g. in 20–50% of advanced cancer patients [8]. However, the diagnosis depends to a great extent on the expertise of the staff, the diagnostic tools and the subtype of delirium [7, 9]. Thus, the aim of this paper is to provide a brief overview of risk factors and preventive measures, current diagnostic procedures, as well as nonpharmacological and pharmacological treatment options for delirium in palliative care that have to be considered depending on patient's state and treatment goals.

Evaluate changes in attention and awareness

According to the eleventh revision of the International Classification of Diseases (ICD-11), delirium is primarily characterized by disturbed attention and awareness. It usually develops over a short period of time and shows fluctuations over the course of a day with more severe symptoms during the evening and the night. Furthermore, it is often accompanied by cognitive impairment such as disorientation, memory deficit, or impairment in language, visuospatial ability, or perception. In addition, disturbance of the sleep–wake cycle may be present [10]. An overview of the diagnostic characteristics of delirium according to ICD-11 and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) are shown in Table 1. Unlike the ICD-11, the DSM-5 also makes the distinction between hyperactive, hypoactive and mixed delirium [11]. While hyperactive and mixed subtypes are more precisely and easily identified due to excessive psychomotor activity, hypoactive delirium is often overlooked, although it may be predominant in palliative care with approximately 40% of delirium patients [1].

It is crucial to identify delirium as soon as possible, as delayed treatment may result in worse outcomes

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Table 1 Diagnostic characteristics of delirium according to ICD-11 and DSM-5 [10, 11]

ICD-11	DSM-5
Delirium is characterized by disturbed attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (i.e. reduced orientation to the environment) that develops over a short period of time and tends to fluctuate during the course of a day , accompanied by other cognitive impairment such as memory deficit, disorientation, or impairment in language, visuospatial ability, or perception. Disturbance of the sleep–wake cycle (reduced arousal of acute onset or total sleep loss with reversal of the sleep–wake cycle) may also be present. The symptoms are attributable to a disorder or disease not classified under mental and behavioural disorders or to substance intoxication or withdrawal or to a medication	<p>A. Disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).</p> <p>B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.</p> <p>C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).</p> <p>D. The disturbances in Criteria A and C are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.</p> <p>E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.</p> <p>Specify if:</p> <p>Hyperactive: The individual has a hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care.</p> <p>Hypoactive: The individual has a hypoactive level of psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor.</p> <p>Mixed level of activity: The individual has a normal level of psychomotor activity even though attention and awareness are disturbed. Also includes individuals whose activity level rapidly fluctuates</p>

Table 2 Guide to preventive, diagnostic and treatment measures (without claiming to be complete)

Steps	What could be done	Examples
Identify patients at-risk of delirium	Information for the team, patients, care givers regarding delirium, its risk factors and its preventive measures	Risk factors: age, CNS tumour, comorbidity, polypharmacy
Screen for delirium	Implement screening tools	CAM
Diagnose	Diagnostic characteristics of DSM-5 and ICD-11	Be aware of hypoactive delirium
Assess (depending on patient's state and treatment goals)	Clinical/physical assessment	Blood pressure, pulse, auscultation, temperature, skin turgor, ...
	Review medication and rule out further causes	DEL-FINE score/1 WATCH DEATH
	Consider appropriate laboratory and radiological investigations	Chest X-ray, urine analysis/urine culture, electrolytes
Treat (depending on patient's state and treatment goals)	Treatment of potentially reversible causes	According to respective guideline
	Non-pharmacological interventions	Support orientation Sleep logs and rhythmic activities Physical therapy Hearing and visual aids Sufficient fluid, balance Integration of relatives
	Pharmacological treatment	Short-term administration of antipsychotics at the lowest effective dose

DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, *ICD-11* eleventh revision of the International Classification of Diseases, *CAM* Confusion Assessment Method, *1 WATCH DEATH* Infections, Withdrawal, Acute metabolic causes, Trauma, CNS pathology, Hypoxia, Deficiencies, Endocrinopathies, Acute vascular, Toxins or drugs, Heavy metals, *CNS* central nervous system

[12]. A number of validated assessment tools are available for screening, the grading of severity and to regularly monitor the illness. However, only a few have been validated for the palliative care setting, including the Confusion Assessment Method (CAM) [13] and the Memorial Delirium Assessment Scale (MDAS) [14]. The CAM is also the most widely used in palliative care and shows the best evidence due to its high sensitivity and specificity [15]. It consists of a nine-item questionnaire and four features diagnostic algorithm: acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness. It requires prior training, takes around five minutes to complete and has to be combined with a test to assess cognitive impairment [16]. Although it is based on the

DSM-III-R, there might be a high agreement between the CAM and the DSM-5 [17].

Consider predisposing and precipitating factors

Delirium is an acute condition in which the identification and treatment of the underlying cause is crucial. While numerous predisposing risk factors such as age, male gender, sensory and cognitive impairments or brain tumours are known to increase the likelihood of disorder onset, precipitating factors like medication or metabolic factors as well as infections can trigger an episode [8]. Studies systematically assessing predisposing and precipitating risk factors in palliative care, especially the outpatient setting, are rare and their results vary. This can be explained by differences in

the methodology as well as by the multifactorial and often nonspecific causes of the disorder. Palliative patients, who in most cases are severely multimorbid and terminally ill, are therefore particularly difficult to examine, since the identification of risk factors is sometimes masked, for example, by high systematic inflammation parameters [18].

As the aetiology is multifactorial and complex the use of guidelines, which will be displayed in more detail in the treatment section, as well as mnemonics like I WATCH DEATH (Infections, Withdrawal, Acute metabolic causes, Trauma, CNS pathology, Hypoxia, Deficiencies, Endocrinopathies, Acute vascular, Toxins or drugs, Heavy metals) are of help to identify the main risk factors in daily practice [19]. Furthermore, the consideration of the three “D”s: dementia, delirium and depression are essential, but also challenged due to an often-unknown cognitive status before admission as well as atypical or overlapping symptoms. However, generally speaking, in contrast to depression and dementia, delirium is characterised by a rapid onset, a high fluctuation of the symptoms during the day, a day night reversal and often a presence of vegetative symptoms.

Focus prevention over treatment

Since there are a number of guidelines, the ESMO Clinical Practice Guidelines on delirium in adult cancer patients can be specifically recommended for palliative settings as guidance in the differential diagnostic clarification [8]. Although management should primarily depend on the course of the disease, the patient’s state and treatment goals, first and foremost, it should be the goal to prevent the occurrence of delirium. Therefore, it is advised to implement any measure that reduces mental or physical stress for patients such as supporting orientation (e.g. hearing/vision aids, tools for orientation in time and place, relative care treatment and family involvement), optimizing the sleep–wake cycle and keeping up mobility [20]. To train caregivers in preventive measures and in basic skills for the immediate detection of delirium is of particular importance in palliative home care settings, since only limited resources for care and diagnostics are available and any further changes in care setting such as the need for hospitalization represents additional risk in itself.

Furthermore, the consideration of the interplay between multimorbidity, frailty and polypharmacy seems to be of particular importance. Hence, paying attention to the medication and avoiding polypharmacy is of high relevance, as many drugs may cause or worsen delirium. Particular care has to be taken with benzodiazepines, opioids and corticosteroids and probably anticholinergics [8, 21]. A helpful tool for the evaluation of the delirogenic potential is the DEL-FINE score. It systematically categorizes substances and substance withdrawal

in relation to their delirogenic potential in order to optimize the medication of vulnerable patients ranging from “three=strong delirogenic potential” to “zero=no delirogenic potential”. A score of three is for example given to the medications: amitriptyline, atropine, clomipramine, orphenadrine, oxybutinin, scopolamine and the withdrawal of benzodiazepines, ethanol and opioids [22].

As opioids play a central role in palliative pain management, it is important to note that there is some evidence that switching the opioid to fentanyl or methadone may improve delirium [23]. Generally speaking, it is worth mentioning that opioids should not be used for sedation, which is a common mistake in clinical practice. Moreover, in case of an identified precipitating cause for delirium such as an infection or electrolyte imbalance, the initiation of adequate therapy according to the respective guidelines should be considered. The chosen treatment should be in concordance with the treatment goals of the patient and include an evaluation of the negative consequences of diagnostic procedures and the potential of reversibility.

Concerning delirium-targeted treatment, prevention by multicomponent nonpharmacological interventions seems to be a cost-effective way to significantly reduce delirium rates and falls. Nonpharmacological interventions address cognition, mobility, oxygen saturation, pain, hydration, sleep–wake cycle and sensory impairment and nutrition [20, 24]. Regarding pharmacological prevention, recent evidence casted doubt on the superiority of antipsychotics and other drugs to placebo [25–28]. Thus, there is only a recommendation for nonpharmacological interventions in people at risk according to the NICE guidelines [29]. Similarly, the evidence for antipsychotics in treatment of delirium is rather limited [25, 30, 31]. Aforementioned studies analysing prevention also did not find a significant improvement in treating delirium. However, the NICE guidelines still recommend short-term use of haloperidol if the patient poses a danger to others or themselves and nonpharmacological interventions have failed [20]. The efficacy is supported by a systematic review of haloperidol [32]. Contrarily, in a randomized clinical trial in a palliative setting haloperidol (and risperidone) worsened symptoms compared to placebo [28]. The ESMO guideline for delirium in cancer patients therefore advised against haloperidol and risperidone, although there is some evidence for olanzapine, quetiapine and aripiprazole to be potentially beneficial [8]. It should also be mentioned that the alpha-antagonist dexmedetomidine showed benefits in the ICU setting [33–35]. In conclusion, the value of antipsychotics and other pharmacological interventions is under debate and physicians should only use them with caution, as antipsychotics are among other things associated with prolongation of the QTc interval, extrapyramidal symptoms (EPS) and worsening of parkinsonian

symptoms. However, when symptomatic treatment of agitation/hyperactivity, anxiety and distress is required, considerate usage of antipsychotics and even benzodiazepines, despite being delirogenic, may be useful.

In summary, rather than treat those already affected, physicians should focus on prevention, early detection and subsequent implementation of non-pharmacological interventions, since treatment options may not be as efficacious as formerly assumed. A practical guide to preventive, diagnostic and treatment measures is summarized in Table 2.

Take home message

- Beware of (hypoactive) delirium as it is rather common and easily missed.
- Target precipitating risk factors and avoid polypharmacy, in particular delirogenic drugs as benzodiazepines, opioids and corticosteroids.
- Use antipsychotics with caution and as short as possible.

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Conflict of interest F. Portela Millinger and M. Fellingner declare that they have no competing interests.

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